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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Fructalate

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Director
Chemicals Notification and Assessment

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Firmenich Limited (ACN 002 964 794)
73 Kenneth Rd Balgowlah NSW 2093

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Chemical name
Other names
CAS number
Molecular formula
Structural formula
Molecular weight
Spectral data
Identity and weight percent of toxic or hazardous impurities
Identity and weight percent of non-hazardous impurities
Identity and weight percent of additives and adjuvants

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Chemical, Permit No. 316, 1999.

NOTIFICATION IN OTHER COUNTRIES

USA	PMN P95-2029	1995
Switzerland		1996
Philippines		2000
Canada	NSN #9626	2001
European Union (UK)		
Annex VII-B	95-06-0733-00	1995
Annex Vii-A	417-310-0	2000

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Fructalate

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD	UV/visible spectrophotometry Infrared (IR) spectroscopy Mass spectroscopy ^{1}H nmr spectroscopy ^{13}C nmr spectroscopy
Remarks	Reference spectra were provided by the notifier.

3. COMPOSITION

DEGREE OF PURITY
Minimum 96 %

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be introduced as a small component (maximum 1 %) of compounded fragrances.

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

Year	*1*	*2*	*3*	*4*	*5*
kilograms	500	600	700	800	900

USE
The notified chemical will be used as a fragrance ingredient in a variey of cosmetic and domestic products. It will be imported in liquid compounded fragrances, which will be reformulated in Australia to produce the final consumer products. In the final products, the concentration of the notified chemical will be a maximum of 0.2 % in fine perfumes, and a maximum of 0.005 % in other cosmetic products and domestic products such as household cleaners.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
The notified chemical is expected to initially be imported through Sydney, by wharf or airport.

IDENTITY OF MANUFACTURER/RECIPIENTS
The fragrance preparations containing the notified chemical will initially be stored and distributed from the notifier's site. The notifier estimated that there will be four customers, in the areas of cosmetic and household product formulation.

TRANSPORTATION AND PACKAGING
The fragrance preparations containing the notified chemical will be transported by road from the wharf or airport to the notifier's site and thence to the customer sites. The fragrance preparations will be imported and distributed in tightly closed lacquered drums, typically of 180 kg size, but also 100, 50, 25 10 or 5 kg. Final consumer products will be sold in a variety of small package sizes.

5.2. Operation Description

The fragrance preparations containing the notified chemical will be reformulated to produce domestic products in a continuous mixing process, which will involve a regulated feed of the fragrance mixture into an automated system. Cosmetic products will be produced in a batch process, which may involve open vessels and manual addition of the notified chemical. Batches will be produced generally once monthly, with fortnightly production on some occasions. Batch sizes will vary with product, but may be of the order of 100 kg.
The products will be distributed to retail outlets, displayed and sold to the public.

5.3. Release

RELEASE OF CHEMICAL AT SITE
Release of the notified chemical to the environment during blending of the cosmetic and household products is expected to be minimal. Potential sources of release include spills, equipment washing, and container residues. The drum size of the fragrance preparation containing the new chemical

will determine the amount of environmental release in the event of an accidental spill. The notifier anticipates a total of 0.1% of waste may be generated as a result of spills. No release is anticipated from cleaning of formulation equipment. It is expected that this equipment will be cleaned using water and the aqueous solution reused for new purposes. The average amount of residue in empty containers after removal by vacuum pump is estimated to be <0.1%. The notifier anticipates a total of 0.2% or up to 1.8 kg of waste generated each year as a result of formulation.

RELEASE OF CHEMICAL FROM USE
Almost all of the notified chemical will enter the aquatic compartment during use of the consumer products into which it is incorporated. Shampoos, perfumes and cosmetic will enter the aquatic environment when washed off the hair and skin during bathing, and cleaning agents will enter the aquatic environment during or after cleaning activities.

5.4. Disposal

Disposal via incineration or landfill is recommended for wastes generated during the formulation of the products containing the fragrance preparation.

6. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa Colourless liquid

FREEZING POINT -12°C

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
TEST FACILITY Safepharm Laboratories Ltd (1995a)

BOILING POINT 276 - 280°C at 100.6 – 103.6 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
TEST FACILITY Safepharm Laboratories Ltd (1995a)

DENSITY 1050 kg/m^3 at 20°C

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Density was measured using the pycnometer method.
TEST FACILITY Safepharm Laboratories Ltd (2000a)

VAPOUR PRESSURE 1.96×10^{-4} kPa at 25°C.

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was measured using a vapour pressure balance over a range of 25 to 35°C and extrapolated back to 25°C. The results indicates the notified chemical is moderately volatile (Mensink e*t al*. 1995).

The Henry's Law constant was calculated from the molecular weight, the measured water solubility, and the vapour pressure according to the following equation: H = MW (g/mol) x Vapour Pressure (Pa)/Water Solubility (mg/L). H = 0.03567 Pa m^3/mol, indicating the chemical is moderately volatile (Mensink e*t al*. 1995).
TEST FACILITY Safepharm Laboratories Ltd (1999a)

WATER SOLUBILITY 1.28 g/L at 20°C

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The water solubility was determined by stirring excess test material into water at 30°C, equilibrating for 24 hours at 20°C, and then separating the aqueous and non aqueous layers by centrifugation and filtration. The concentration of the test substance in the aqueous phase was determined spectrophotometrically and the average of 3 determinations taken as the solubility.

TEST FACILITY Safepharm Laboratories Ltd (1995a)

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*	$t_{½}$
4	25	> 1 year
7	25	> 1 year
9	25	228 hr

Remarks Analytical Method: Gas chromatography
Rate constants were determined at 40ºC and 50ºC and the $t_{1/2}$ values at 25ºC were obtained by extrapolation.
TEST FACILITY Safepharm Laboratories Ltd (2000a)

PARTITION COEFFICIENT (n-octanol/water) log Pow at 30ºC = 3.04 to 3.19

METHOD OECD TG 117 Partition Coefficient (n-octanol/water), HPLC Method.
Remarks The n-octanol/water partition coefficient was determined using the HPLC screening method, where the retention times of the test material on C8-18 columns is compared with those of 8 reference substances with known Kow values ranging from 1.1 (benzyl alcohol) to 6.2 (DDT). The results indicate the notified chemical has an affinity for organic matter in the environment.
TEST FACILITY Safepharm Laboratories Ltd (1995a)

ADSORPTION/DESORPTION log K_{oc} = 2.58.

METHOD EC Directive 93//67/EEC
Remarks The log Koc was calculated using QSAR (quantitative structure-activity relationships) for esters. The method is recommended by the EEC to calculate the Koc of various classes of organic compounds (European Commission, 1996). For esters the QSAR is calculated as follows: logKoc = 0.49 log Pow + 1.05 = 2.58. Based on this estimate, according to the mobility scale of McCall *et al*. (1980), the chemical will have medium mobility in soils. Thus some adsorption may be expected.
TEST FACILITY Safepharm Laboratories Ltd (2000a)

DISSOCIATION CONSTANT

Remarks Not determined. There are no acidic or basic groups on the molecule able to dissociate

SURFACE TENSION 50.7 mN/m at 21.5ºC

METHOD EC Directive 92/69/EEC A.5 Surface Tension
Remarks Concentration: 1.14 g/L
Test was performed using the ISO 304 ring method. The results of the test were considered unexpected as the structure does not indicate surface activity, and the result is not explicable in terms of hydrolysis during the procedure. The test facility indicated that the solution does not appear to have typical surfactant properties such as emulsifying oil/water mixtures.
TEST FACILITY Safepharm Laboratories Ltd (2000a)

PARTICLE SIZE

Remarks Test not conducted as the notified chemical is a liquid.

FLASH POINT 141 ± 2ºC at 101.3 kPa

METHOD EC Directive 92/69/EEC A.9 Flash-Point
TEST FACILITY Safepharm Laboratories Ltd (1995b)

FLAMMABILITY LIMITS

Remarks Test not conducted. The low vapour pressure indicates that the flammability limits are not likely to be reached under normal environmental conditions.

AUTOIGNITION TEMPERATURE 384°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
TEST FACILITY Safepharm Laboratories Ltd (1999b)

EXPLOSIVE PROPERTIES Not explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties
Remarks A negative result was obtained for sensitivity to shock and to heat. The test for friction sensitivity is not applicable to liquids.
TEST FACILITY Safepharm Laboratories Ltd (1999b)

REACTIVITY

Remarks The notified chemical is expected to be stable under normal environmental conditions. No test of oxidising properties was performed, as the test method is not applicable to liquids; however the notified chemical does not have any structural indications of oxidising properties or other unusual reactivity.

7. TOXICOLOGICAL INVESTIGATIONS

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD 420 Acute Oral Toxicity - Fixed Dose Method.
EC Directive92/69/EEC B.1bis Acute Toxicity (Oral) Fixed Dose Method.
Species/Strain Rat/Crl: CD(SD)BR (VAF Plus)
Vehicle 0.5 % carboxymethyl cellulose
Remarks - Method No significant protocol deviations.

RESULTS

Sighting Study

Dose mg/kg bw	*Administered*	*Evident Toxicity*	*Mortality*
2000	1	0/1	0/1
500	1	0/1	0/1

Signs of Toxicity No clinical signs of toxicity were observed.

Main Study

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

Discriminating Dose 2000 mg/kg bw
Signs of Toxicity No clinical signs of toxicity were observed. No effect on bodyweight gain was seen.
Effects in Organs The submandibular lymph nodes were swollen in one male. No other

	macroscopic abnormalities were seen at necropsy.
Remarks - Results	

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

TEST FACILITY Toxicol Laboratories Ltd (1994a)

7.2. Acute toxicity - dermal

TEST SUBSTANCE Notified chemical

METHOD OECD 402 Acute Dermal Toxicity – Limit Test.
EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.

Species/Strain	Rat/Sprague-Dawley CD (Crl: CD(SD)IGS BR)
Vehicle	Used as supplied.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No signs of irritation were observed.
Signs of Toxicity - Systemic	No clinical signs of systemic toxicity were observed. No effect on bodyweight gain was seen.
Effects in Organs	No macroscopic abnormalities were seen at necropsy.
Remarks - Results	

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

TEST FACILITY Safepharm Laboratories Ltd (1999c)

7.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD EC Directive 92/69/EEC L383A.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 female
Vehicle	Used as supplied.
Observation Period	7 days
Type of Dressing	Semi-occlusive.
Remarks - Method	One animal was treated initially as a pilot. For the remaining animals, the observation time was extended to 7 days as effects were present after 3 days.

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	0	1.3	2	2	72 hr	0
Oedema	0	0.3	0	1	24 hr	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 skin.
TEST FACILITY	Toxicol Laboratories Ltd (1994b)

7.4. Irritation - eye

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC O.J. L383A
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 female
Observation Period	3 days
Remarks - Method	One animal was treated initially as a pilot.
RESULTS	
Remarks - Results	All Draizes scores for conjunctival, iridal and corneal effects were zero from 24 hr to the end of the study. Very slight conjunctival hyperaemia (redness) was observed at 1 hr in all animals, clearing by 24 hr.
CONCLUSION	The notified chemical is non-irritating to the eye.
TEST FACILITY	Toxicol Laboratories Ltd (1994c)

7.5. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC O.J. L383A Maximisation Test
Species/Strain	Guinea pig/Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 10 % (erythema only observed) topical: 100 %
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
induction phase	Induction Concentration: intradermal injection 10 % in light paraffin topical application 100 %
Signs of Irritation	No details of irritation responses during induction were reported.
CHALLENGE PHASE	
1st challenge	topical application: 100 %
Remarks - Method	One day prior to topical induction, irritation was induced by application of sodium lauryl sulphate in light paraffin
RESULTS	
Remarks - Results	All irritation scores in both test and control animals were zero during the challenge phase.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Toxicol Laboratories Ltd (1994d)

7.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/Sprague-Dawley Crl:CDBR
Route of Administration	Oral – gavage.
Exposure Information	Total exposure days: 28 days; Dose regimen: 7 days per week.
Vehicle	arachis oil BP
Remarks - Method	Histopathological examinations were performed on a wide range of tissues from Group I and IV animals; the liver, spleen and any macroscopic lesions from Group II and II animals were examined.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I	5 per sex	0	0/10
II	5 per sex	15	0/10
III	5 per sex	150	0/10
IV	5 per sex	1000	0/10

Mortality and Time to Death

There were no unscheduled deaths during the study.

Clinical Observations

No clinical signs of systemic toxicity were observed in treated animals. Increased salivation was noted after dosing in Group IV animals. Behavioural, functional and sensory response observations showed no treatment related effects. A single functional parameter, the forelimb grip strength in females of Group IV, showed a significant increase compared with controls. Food and water consumption and body weights were generally not affected by treatment, although the Group IV females showed a statistically significant reduction in body weight gain during week 3.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No urinalysis results were reported. Haematological parameters showed no statistically significant differences between controls and any of the treated groups. Several clinical chemistry parameters were significantly different in Group IV animals compared with controls, while no significant differences were seen in Group II or III animals.

Group IV males showed increased plasma creatinine and reduced plasma glucose, while the females showed reduced potassium and increased inorganic phosphorous. Apart from the difference in creatinine, the differences were not reflected in the lower dose groups or animals of the other sex. While not statistically significant, the creatinine level for Group IV females was higher than for the controls, and in all treated animals, very small non-significant increases relative to controls were seen.

Effects in Organs

No statistically significant effects on absolute or relative organ weights were observed. No gross abnormalities were observed at necropsy in any group. The observed histopathological lesions were limited to isolated occurrences, or occurred at similar incidence in Groups I and IV.

Remarks – Results

Almost all of the differences discussed above occurred only in single groups, without confirmation from the other sex in the same group, or from other treated animals. While there is an appearance of a dose-response for creatinine concentration, the differences are at most barely significant, and no corresponding change in plasma urea or kidney histopathology was seen to indicate kidney dysfunction.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 1000 mg/kg bw/day in this study, based on the lack of dose dependent statistically significant changes in any of the observed parameters.

TEST FACILITY Safepharm Laboratories Ltd (2000b)

7.7. Genotoxicity - bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B. 14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100.
Metabolic Activation System	10 % rat liver S9 fraction from animals pretreated with Aroclor 1254
Concentration Range in Main Test	a) With metabolic activation: 50 – 5000 µg/plate. b) Without metabolic activation: 15 – 5000 µg/plate.
Vehicle	acetone
Remarks - Method	Two separate experiments were performed in triplicate.

RESULTS

Remarks - Results No substantial increases in the number of revertant colonies were seen in any strain either in the presence or absence of metabolic activation. Toxicity, in the form of reduced background lawn, was seen for all strains at 5000 µg/plate in the absence of metabolic activation.
Appropriate positive controls induced large increases in the number of revertant colonies, indicating that the test system responded appropriately.

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

TEST FACILITY Safepharm Laboratories Ltd (1995c)

7.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD 473 In vitro Mammalian Chromosomal Aberration Test.

Cell Type	Human lymphocytes
Metabolic Activation System	Rat liver S9 fraction from animals pretreated with phenobarbitone and β-naphthoflavone.
Vehicle	dimethyl sulphoxide (DMSO)
Remarks - Method	Tests were performed in duplicate. No preliminary test was reported.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1	0*, 17.81, 35.63, 71.25, 142.5, 285, 570*, 1140*, 2280*	4 hr	20 hr
Test 2	0*, 17.81, 35.63, 71.25, 142.5, 285, 570*, 1140*, 2280*	4 hr	20 hr
Absent			
Test 1	0*, 17.81, 35.63, 71.25, 142.5, 285, 570*, 1140*, 2280*	4 hr	20 hr
Test 2	0*, 17.81, 35.63, 71.25*, 142.5*, 285*, 570, 1140, 2280	20 hr	20 hr

*Cultures selected for metaphase analysis.

RESULTS

Remarks - Results Cytotoxicity as measured by reduction in mitotic index was significant in the absence of metabolic activation at 1140 µg/mL for 4 hr (Test 1) and 285 µg/mL for 20 hr (Test 2).
No statistically significant increases in the frequency of chromosome aberrations or polyploidy were observed either in the presence or

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

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

TEST FACILITY Safepharm Laboratories Ltd (1999d)

8. ENVIRONMENTAL EFFECTS

8.1. Ecotoxicological investigations

8.1.1. Acute toxicity to fish

TEST SUBSTANCE ST 03 C 99, colourless liquid

METHOD OECD TG 203 Fish, Acute Toxicity Test –semi static conditions
Species Rainbow Trout *(Oncorhynchus mykiss)*
Exposure Period 96 hours
Auxiliary Solvent None
Water Hardness 100 mg $CaCO_3$/L
Analytical Monitoring Gas Chromatography to verify test concentrations.
Remarks – Method The stock solution was prepared by adding test material directly to water, the solution was ultrasonified, shaken for 30 minutes, and then the volume adjusted to the required concentrations. The pH of the test media ranged from 7.2-7.5 and dissolved oxygen from 7.8 to 9.8 mg/L. The headspace in the test vessel was reduced to prevent loss of test material by evaporation from the test media. Test concentrations were verified at 0, 24, and 96 hours and were maintained between 90 and 122% of nominal.

RESULTS The highest test concentration resulting in 0% mortalities was 3.2 mg/L, the highest concentration resulting in 100% mortalities was 10 mg/L. Sublethal effects were observed at test concentrations of 3.2 mg/L and above. Sublethal responses were: swimming at the bottom of the test vessel, swollen abdomen, and increased pigmentation.

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1h*	*24h*	*48h*	*72h*	*96h*
1.0	0.98-1.2	10	0	0	0	0	0
1.8	1.63-2.2	10	0	0	0	0	0
3.2	3.13-3.82	10	0	0	0	0	0
5.6	5.52-6.22	10	0	0	0	1	1
10	9.52-11.7	10	0	0	10	10	10

LC50 >10 mg/L at 24 hours.
7.5 mg/L at 48 hours.
7.1 mg/L at 72 hours.
7.1 mg/L at 96 hours.
NOEC 1.8 mg/L at 96 hours.
Remarks – Results The LC50 values and confidence limits at 72 and 96 hours were calculated using the trimmed Spearman-Karber method of Hamilton *et al* (1997).

CONCLUSION The results of the acute toxicity test indicate the test material is moderately toxic to fish (Mensink *et al.* 1995)

TEST FACILITY Safepharm Laboratories Ltd (1999e)

8.1.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	ST 03 C 99, colourless liquid
METHOD	OECD TG 202 *Daphnia Magna*. Acute Immobilisation Test – static test conditions.
Species	*Daphnia magna*
Exposure Period	48 hours *[acute study]*
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography to verify test concentrations
Remarks - Method	The stock solution was prepared by adding test material directly to reconstituted water, the solution was ultrasonified, shaken for 20 minutes, and then the volume adjusted to the required concentrations. The test vessels were filled and sealed to prevent loss of test material by evaporation. Test concentrations were verified for selected sample concentrations at 0 and 48 hours and were maintained between 80 and 114% of nominal.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
1.0	0.82-1.1	20	0	0
1.8		20	0	0
3.2	2.57-3.65	20	0	0
5.6		20	0	0
10	8.11-10.4	20	0	0
18		20	0	0
32	27.8-28.9	20	0	5
56		20	0	13
100	90.2-92.7	20	15	20

LC50	82 mg/L at 24 hours *[acute]* 45 mg/L at 48 hours *[acute]*
NOEC	18 mg/L at 48 hours *[acute]*
Remarks - Results	No immobilisation of daphnia was observed at test concentrations below 18 mg/L. At concentrations of 32 mg/L, 25% of daphnids were immobilised after 48 hours, at 56 mg/L, 65% of daphnids were immobilised after 48 hours, and at 100 mg/L, 100% of daphnids were immobilised after 48 hours of exposure. The test results indicate that the notified chemical is slightly toxic to *Daphnia magna* (Mensink *et al*. 1995).
CONCLUSION	The EC50 values were analysed using the trimmed Spearman-Karber method (Hamilton *et al*. 1977) at 24 hours and the Probit method (Finney 1971) at 48 hour. The chemical is slightly toxic to freshwater invertebrates.
TEST FACILITY	Safepharm Laboratories Ltd (1999f)

8.1.3. Algal growth inhibition test

TEST SUBSTANCE	ST 03 C 99, colourless liquid
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours

Concentration Range (Nominal)	6.25, 12.5, 25, 50 and 100 mg/L
Concentration Range (Actual)	90 to 111% nominal
Analytical Monitoring	Cell density counted with Coulter Multisizer II Particle Counter CPC analyses to verify test concentrations
Remarks - Method	Tests were carried out in closed flasks covered with foil to reduce evaporation. The test substance was dissolved in the sample medium with the aid of ultrasonification (15 min) and the volume adjusted to the required concentrations. Concentrations were verified at 0 and 72 hours and were found to range from 90 to 111% of nominal. The concentration resulting in a 50% reduction in biomass was determined by reading from the plot of the area under the growth curve at 72 hours. The concentration resulting in a 50% reduction in growth rate was calculated by comparing the difference in area under the growth curve of the algae cells exposed to the test substance with the growth of cells in the control.

RESULTS

Biomass		*Growth*	
EbC50 *mg/L at 72 h*	*NOEC* *mg/L*	*ErC50* *mg/L at 0-72 h*	*NOEC* *mg/L*
58 mg/L	25	86	25

Remarks - Results	Both the growth rate and biomass were affected by the presence of the test material over the exposure period. No physical abnormalities were observed in test cultures exposed to 6.25, 12.5, 25, and 50 mg/L, however, cell debris was observed in the culture medium exposed to 100 mg/L of test material.
CONCLUSION	The test substance is slightly toxic to algae (Mensink *et al*. 1995).
TEST FACILITY	Safepharm Laboratories Ltd (1999g)

8.1.4. Inhibition of microbial activity

TEST SUBSTANCE	ST 03 C 99, colourless liquid
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge microorganisms from domestic sewage
Exposure Period	3 hours
Concentration Range Nominal	100, 180, 320, 560 and 900 mg/L
Remarks – Method	A rangefinding test was performed using concentrations of 1, 10, 100 and 1000 mg/L test substance. To prepare the stock solution, the test substance was dissolved directly in water. At concentrations in excess of 1 g/L the test material was observed to form a cloudy dispersion and not a solution. To minimise dilution of test media by addition of sewage sludge, the activated sludge was centrifuged and the supernatant discarded prior to addition to test vessels.
RESULTS	
EC50	3 h EC50 = 840 mg/L
NOEC	320 mg/L
Remarks – Results	The maximum attainable test concentration was 900 mg/L upon addition of the synthetic sewage and activated sludge, hence the definitive test was based on a maximum test concentration of 900 mg/L

CONCLUSION	The test substance is very slightly toxic to microorganisms (Mensink *et al*. 1995).
TEST FACILITY	Safepharm Laboratories Ltd (1999h)

8.2. Environmental fate

8.2.1. Ready biodegradability

TEST SUBSTANCE	ST 02 C 94, colourless liquid
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved oxygen (Yellow Springs BOD probe and oxygen meter).
Remarks - Method	Test species were a mixed population of activated sludge microorganisms from predominantly domestic sewage treatment plant. Microorganisms were exposed to test concentrations of 2 mg/L.

RESULTS

ST 02 C 94		*Sodium Benzoate*	
Day	*% degradation*	*Day*	*% degradation*
9	17	9	43
28	34	28	81

Remarks - Results	The test substance attained 34% degradation after 28 days and therefore cannot be considered readily biodegradable under OECD guidelines requiring >60% degradation by day 28. The toxicity control attained 47% degradation after 28 days indicating the test substance was not toxic to the sewage microorganisms. The standard material attained 81% degradation indicating the viability of the culture and test conditions.
CONCLUSION	The notified chemical is not readily biodegraded by sewage microorganisms.
TEST FACILITY	Safepharm Laboratories Ltd (1995d)

8.2.2 Bioaccumulation

No bioaccumulation data were provided in the notification dossier. While the chemical structure, molecular weight, water solubility, and Pow of the notified chemical suggest a potential for the notified chemical to cross biological membrane and bioaccumulate (Connell, 1990), this is not likely to occur due to the expected ready metabolism of the ester groups.

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

Only a small amount of the notified chemical will be released into the environment as a result of the formulation of cosmetic and cleaning products containing the notified chemical. Ultimately, however, all of the chemical will be released into the aquatic environment at end use via sewage treatment facilities either when the cosmetics are washed off the skin or when cleaning agents are used during cleaning activities.

The notified chemical is highly water-soluble and hence, in sewage treatment plants, is

expected to partition mainly into the water compartment. The partition coefficient indicates the chemical has some affinity for organic matter in the environment, and some adsorption onto sewage sludge can also be expected. The vapour pressure and Henry's Law Constant indicate the chemical is moderately volatile, suggesting some partitioning into the atmosphere from water will also occur.

Mackay Level 1 fugacity modelling using the variables: molecular weight, Log K_{ow}, water solubility, Henry's Law Constant, vapour pressure and melting point, indicate that when the notified chemical is released into the environment, 81 % will partition into the air, 11% will partition into soil, and 8 % will enter the water compartment. In contrast, information provided in the notification dossier using the SIMPLETREAT model (EC 1996), indicates that when the chemical is released into the aqueous phase of a waste-water treatment facility, 87.5 % will partition into water, 12 % will partition into sludge, and 0 % will partition into air. In the latter model, the fate was determined using only Log H = –1.45 and Log P_{ow} = 3.115 and assuming no biodegradation. The percentages were calculated from the arithmetic mean of the tabulated values between Log H –1 to –2 and Log P_{ow} 3 to 4, since the table does not allow for decimals.

The large differences given by each model in the percentages of chemical going to the water and the atmosphere is mainly due to difference in the number of variables used in the calculations between each model. Because we are concerned mainly with deriving worst case scenario Predicted Environmental Concentration (PEC) for the aquatic compartment (where release will occur), the PEC values that follow are calculated using the values from the SIMPLETREAT model. However, it is likely that this model has underestimated the amount of chemical partitioning into the atmosphere.

A worst case scenario daily PEC for the local aquatic environment resulting from formulation of products containing the notified chemical was also provided by the notifier. Household cleaning products were used as an example because they contain the highest concentrations of the notified chemical. The parameters used to calculate the PEC are as follows:

Batch Size of household detergent product: 1 tonne/day = 1×10^9 mg/day
Percentage of chemical in final product: 0.005% = 5×10^{-5}
Chemical to waste: 0.2% = 0.002 (default value)
Proportion to water in WWTP: 87.5% = 0.875 (from SIMPLETREAT model)
Flow in WWTP: 2000 m^3 /day = 2×10^6 L/d (default value)
Dilution by surface water: 10 (default value)
Daily PECaquatic: 4.375×10^{-6} mg/L

A worst case scenario daily PEC for the aquatic environment resulting from release at end use of products containing the notified chemical is provided below and is a modified version of the one provided in the notification dossier. In calculating the PEC, we have assumed that release of the notified chemical to sewage systems occurs on a nationwide basis and is continuous throughout the year. While it is recognised that larger releases of the chemical are likely to occur in higher population areas where usage rates would be higher, it was not considered practical to determine such releases for end use. The following additional assumptions were also made:

- All of the 900 kg of chemical imported in one year is released into the sewer over a 365 day period, with no removal of the chemical by adsorption or degradation, giving a daily release of 2500 g.

- Release is distributed throughout the whole country, with a sewer output based on 18 million people using water at an average volume of 150 L per day per person, giving a daily sewer out put of 2700 ML.

The nationwide PEC of the notified chemical at end use is 9.3×10^{-4} mg/L (or 0.9 µg/L) per day. Adsorption of the chemical onto sewage sludge, as indicated by the SIMPLETREAT model calculation, would reduce the PEC by a further 12%. The PEC would also be diluted when released into the receiving waters by an amount that will depend on the nature of the receiving waters (eg. ocean, river, flow rate).

According to the SIMPLTREAT model, about 12% of the notified chemical may partition onto sludge in sewage treatment facilities. Hence about 110 kg of notified chemical could enter the soil environment each year through disposal of sludge in landfill or on agricultural land.

A PEC for sludge and local soil arising from the formulation process was provided in the notification dossier, using the following parameters:

Batch Size of household detergent product: 1 tonne/day = 1 x 10^9 mg/day
Percentage of chemical in final product: 0.005% = 5 x 10^{-5}
Chemical to waste: 0.2% = 0.002 (default value)
Proportion to sludge in WWTP: 12.5% = 0.125 (from SIMPLETREAT model)
Population served by WWTP: 10000 = 10^4 (default value)
Per capita sludge dry solids: 0.06 kg/hd/day (default value)
Sewage sludge application for agricultural soil: 5 ton/ha
Soil dry weight (arable): 3000 ton/ha
PEC Sludge: 0.0208 mg/kg
PEC Local Soil: 3.5 x 10^{-5} mg/kg

9.1.2. Environment – effects assessment

The results of the ecotoxicological data indicate the notified chemical was slightly to moderately toxic to aquatic organisms. The most sensitive species were fish, where the 96 hour LC50 was 7.1 mg/L and the NOEC was 1.8 mg/L.

A predicted no effects concentration (PNEC) can be determined when at least one acute LC50 for each of the three trophic levels is available (ie. fish, Daphnia, algae). The PNEC is calculated by taking the LC50 value of the most sensitive species, and dividing this value by an assessment safety factor of either 100 (OECD) or 1000 (EU). Using a worst case scenario safety factor of 100, the PNECaquatic is 0.071 mg/L.
No ecotoxicological data was provided for terrestrial organisms. The activated sewage sludge inhibition test gave a 3-hour EC50 of 840 mg/L and an NOEC of 320 mg/L, using these data, and an assessment factor of 100, the PNEC for sludge is 8.4 mg/L.

9.1.3. Environment – risk characterisation

The notified chemical was not toxic to sewage microorganisms. However, in sewage treatment systems, the chemical is not expected to readily biodegrade. Only 34% of the test material was degraded after 28 days in a ready biodegradability test (OECD TG 301D) using mixed populations of micro-organisms from domestic sewage sludge. Despite this the PEC/PNEC for a local sewage treatment plant arising from formulation of products containing the fragrance was significantly less than 1 (5.2 X 10^{-6}), hence there is no immediate concern for these organisms.

The static toxicity tests indicate the notified chemical is moderately toxic to fish, and slightly toxic to freshwater invertebrates and algae. However, usage patterns indicate that the concentration of the chemical likely to be encountered by organisms in the aquatic environment will be very low owing to the small amount of chemical in the end products and to the very high dilution rates involved in the release processes. The calculated PEC values are several orders of magnitude lower than the lowest concentrations found to be toxic to aquatic organisms.

The PEC/PNEC ratio for the local aquatic environment as a result of formulation is 6.2 x 10^{-5} and the PEC/PNEC ratio for the aquatic environment, assuming nationwide use, is 0.013. These values are significantly less than 1, indicating no immediate concern to the aquatic compartment.

No terrestrial toxicity data were provided in the notification dossier. Only a relatively small amount of the notified chemical is expected to enter the soil environment via disposal of sewage sludge or residual wastes containing the chemical. In soil environments, the notified chemical will have medium mobility in soils. Thus some adsorption onto organic matter may also be expected as indicated by the adsorption coefficient (Koc). The PEC for local soil is low

and hence there is no immediate concern toward terrestrial organisms.

The chemical is not readily biodegraded or hydrolysed, however, once released into the environment the chemical is not expected to persist, but to undergo eventual degradation by biotic and abiotic processes. The notified chemical contains ester functional groups, which are amenable to hydrolysis and whose hydrolysis may contribute to abiotic breakdown in the environment. Results from the hydrolyses test indicate breakdown will be faster in alkaline (pH > 9) environments. Microorganisms are also expected to play a key role in the breakdown of the chemical. It is likely that microbial degradation rates will increase in sewage treatment facilities where microbes are acclimated to the notified chemical.

While the chemical structure, molecular weight, water solubility, and Pow of the notified chemical suggest a potential for the notified chemical to cross biological membrane and bioaccumulate (Connell 1990), this is not likely to occur due to the expected ready metabolism of the ester groups.

Given the above considerations, the notified chemical is not expected to pose any significant hazard to the environment. The low import volumes and the anticipated nationwide use of the product indicate that the levels of release of the chemical to the environment will be low, and significantly lower than the levels of exposure shown to be toxic to aquatic organisms.

9.2. Human health

9.2.1. Occupational health and safety

9.2.1.1 OCCUPATIONAL EXPOSURE ASSESSMENT

Occupational exposure to the notified chemical may occur during transport and storage, reformulation and testing of fragrance preparations containing the notified chemical at up to 1 %. The notifier stated that between 5 to 20 workers, including warehouse workers, production workers and laboratory workers, could be potentially exposed to the notified chemical, and the duration of worker exposure could be estimated at several minutes per batch. There may also be occupational exposure to consumer products for a large number of workers handling the finished products in the distribution and retail sectors.

Transport workers and storemen are unlikely to be exposed to the notified chemical except when packaging is accidentally breached. The notified chemical will be stored at the notifier's site and transferred to customer sites for reformulation.

The notifier anticipates that reformulation would be carried out predominantly in closed systems, and that addition of the notified chemical would generally not be by purely manual means. Exposure to fragrance preparations containing the notified chemical is possible when opening and closing drums, weighing and charging them to the blending vessel, mixing in open vessels and cleaning operations Exposure to the consumer products, containing a maximum of 0.2 % notified chemical, may also occur due to drips and spills at the filling station.

Workers handling consumer products during distribution and retail would not be expected to be exposed to the notified chemical except in the event of an accident.

Processing is normally carried out in closed systems. If open vessels are used for mixing, adequate ventilation should be provided to remove aerosols that may arise during the process. All workers handling perfume preparations containing the notified chemical and involved in open mixing operations should wear suitable gloves, eye and face protection and protective clothing.

9.2.2. Public health

It is expected that during import, transport, storage, reformulation and manufacture of consumer products, exposure of the general public to the notified chemical will be low, except in the event of an accidental spill.

Consumer products containing the notified chemical, including cosmetics, toiletries, and

household cleaning products, will be sold in the public domain, consequently there is the potential for widespread public exposure. Exposure is likely to be by dermal, inhalation, oral and ocular exposure.

9.2.3. Human health - effects assessment

9.2.3.1 SUMMARY OF TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 > 2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2000 mg/kg bw	low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation - adjuvant test	no evidence of sensitisation.
Rat, oral Repeat Dose Toxicity - 28 Days.	NOEL = 1000 mg/kg bw/day
Genotoxicity - bacterial reverse mutation	Non mutagenic
Genotoxicity – in vitro chromosome aberration test	Non genotoxic

9.2.3.2 DISCUSSION

The notified chemical has low acute toxicity by the oral and dermal routes. It is a slight skin irritant, possibly due to defatting, but not irritating to eyes beyond slight redness on instillation, or sensitising to skin. In a 28-day oral repeat dose study, no differences from controls were consistent across the sexes or clearly dose dependent. All differences from controls were slight, and the NOEL is therefore set at 1000 mg/kg bw/day (the highest dose tested). In two in vitro genotoxicity studies, negative results were obtained.

The notifier indicated that there is no information which indicates that the notified chemical has health effects in humans, based on overseas experience, and also use in Australia under a permit.

9.2.4. Human health – risk characterisation

9.2.4.1 OCCUPATIONAL HEALTH AND SAFETY

Occupational exposure to the notified chemical in fragrance preparations is expected to be very limited, due to the low concentration of the notified chemical present in these. The use of the fragrance preparations will generally be automated, limiting exposure to dermal contact with small quantities of the preparations. While the notified chemical is a slight skin irritant, the concentration handled in the reformulation activities in Australia is not expected to result in significant occupational risk. The presence of a wide range of additional ingredients in the preparations may require that more stringent precautions be taken to prevent worker exposure. Consumer products contain smaller proportions of notified chemical, and the occupation risk posed by the notified chemical in these products is expected to be low. The use of enclosed systems or exhaust ventilation, as well as the personal protective equipment specified in the Material Safety Data Sheet (MSDS), should ensure that the occupational risk posed by the notified chemical is low when used as specified in the notification.

9.2.4.2 PUBLIC HEALTH

It is expected that public exposure to compounded fragrances containing ≤ 1 % Fructalate 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 cosmetics, toiletries, and household cleaning products containing up to 0.2 % of the notified chemical. Although the notified chemical caused slight skin irritation, the irritation hazard posed by consumer products containing ≤ 0.2 % of the notified chemical are likely to be minimal. Consequently the public hazard 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. Environment

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.

10.2. Health hazard

Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

10.3. Human health

10.3.1. Human health – Occupational health and safety

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

10.3.2. Human health – public

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

11. RECOMMENDATIONS

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Local exhaust ventilation should be employed if reformulation is carried out in open systems.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Gloves (natural rubber), safety goggles and industrial clothing and footwear should be worn.

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

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

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

Disposal

- The notified chemical should be disposed of by incineration or landfill.

Emergency procedures

- Spills/release of the notified chemical should be handled by containing spills with sand or inert powder, and disposing of the material in accordance with Government Regulations.

11.1. 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.

12. MATERIAL SAFETY DATA SHEET

The MSDS for the notified chemical was provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994).

This MSDS was provided by the applicant as part of the notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

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