File No: LTD/1325

October 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

3-Decen-5-one, 4-methyl-, (3E)-

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Water Resources.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

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

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

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

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
US (PMN, 2006)
Canada (2006)

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
3-Decen-5-one, 4-methyl-, (3E)-

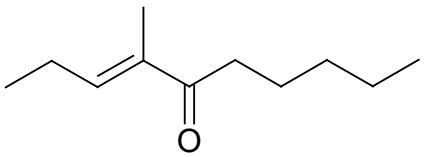
OTHER NAME(S)
Undecavertol Ketone

MARKETING NAME(S)
Methyl decenone

CAS NUMBER
811412-48-3

MOLECULAR FORMULA
$C_{11}H_{20}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
168.27

ANALYTICAL DATA
Reference NMR, IR, GC, UV and MS spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
90%

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	3-decen-5-ol, 4-methyl		
CAS No.	81782-77-6	*Weight %*	10

4. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa Clear liquid

Property	Value	Data Source/Justification
Freezing Point	< -25°C	Measured
Boiling Point	228°C at 101.3 kPa	Measured
Density	850 kg/m^3 at 20°C	Measured
Vapour Pressure	1.52 kPa at 25°C	Measured
Water Solubility	0.055 g/L at 20°C	Measured by flask method
Hydrolysis as a Function of pH	Hydrolytically Stable at pH 4-9	Measured (OECD TG 111)
Partition Coefficient (n-octanol/water)	log P_{ow} = 4.4 at 20°C	Measured by HPLC
Adsorption/Desorption	log K_{oc} = 3.0 at 20°C	Measured by HPLC
Dissociation Constant	Not Determined	There are no chemical groups capable of ionisation in the pH range 4-9
Particle Size	Not determined	Liquid under conditions of use
Flash Point	96°C at 101.3 kPa	Measured
Flammability	Not determined	Based on the measured flash point the notified chemical is not expected to be flammable.
Autoignition Temperature	262°C	Measured
Explosive Properties	Not explosive	Estimated based on chemical structure
Oxidising Properties	Not oxidising	Estimated based on chemical structure
Surface tension	50 mN/m at 20°C	Measured (OECD 115)

Discussion of Observed Effects

For full details of the physical-chemical properties tests please refer to Appendix A.

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

Dangerous Goods classification
Based on the available physico-chemical properties the notified chemical is not classified as a Dangerous Good according to the Australian Dangerous Goods Code (FORS, 1998). However, based on the flash point the notified chemical would be classified as a C1 combustible liquid.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as part of a finished fragrance oil (10% maximum) or in an end-use consumer product at concentrations ranging from 0.01 to 1%.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notifier has indicated that the notified chemical is likely to be imported at < 100 kg/year. However the maximum volume allowed for this notification category is indicated below and is used in the risk assessment.

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

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours and Fragrances (Australia), Pty Ltd. (IFF)

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as a component of finished fragrance oils in sealed, polypropylene lined steel drums (205 L) or as a component of finished consumer products in standard consumer packagings. Notified chemical will be transported from the docks by road to the notifiers warehouse. The finished fragrance oil will then be transported to customers, typically by road, when needed. The finished consumer product will be transported to retails stores for distribution.

USE
The notified chemical will be used as an odourant in alcoholic perfumery, cosmetics, toiletries, household products, soaps and detergents.

The concentration of notified chemical in a finished fragrance oil is a maximum of 10%. The resulting concentration of notified chemical in end-user consumer products is 0.01-1%

The consumer product categories likely to contain the fragrance containing the notified chemical, and the maximum concentration of the notified chemical likely to occur in each product category were provided by the notifier and are presented in the table below. The notifier did not indicate that this is an exhaustive list.

Product Type	% of Fragrance (typical)	% of the Notified Chemical (typical)
Cosmetics/Personal care products		
Leave-on		
Body lotions	0.4	0.04
Face Creams	0.3	0.03
Sun creams/lotions	0.4	0.04
Hairsprays	0.5	0.05
Deodorant sprays	1.0	0.1
Wash-off		
Shampoos	0.5	0.05
Bath products	2.0	0.2
Shower gels	1.2	0.12
Fragrance		
Air fresheners (sprays)	5.0	0.5
Toilet waters	8.0	0.8
Household products		
Dishwashing liquid	0.2	0.02

Fabric washing liquid	0.8	0.08
Surface cleansers	0.6	0.06

It should be noted that the assessment report does not cover products with therapeutic uses, for example, the majority of sunscreens.

OPERATION DESCRIPTION

Formulation

The drummed fragrance oil will be used in the cosmetic industry for production of toiletries, shampoos, soap and household cleaning agents and detergents (containing ≤ 1% notified chemical) following mixing with other ingredients. The production process, mainly involving a blending operation, will be highly automated and will occur in a fully enclosed environment. Plant operators will only be involved in opening and closing drums, weighing and charging the mixing vessel, and cleaning and maintenance tasks. Waste will generally be disposed of by incineration or through a wastewater treatment plant prior to release to the environment.

End use

There is potential for the formulated cleaning products (containing 0.01%) to be used occupationally, for example by professional cleaners using cleaning products or beauticians using cosmetic products.

Cleaning products are generally applied with a cloth or sponge, by mop or brush or by spray followed by wiping. In some cases, the cleaning product will be diluted with water prior to application. The dilution factor, which is often on the label, depends on the type of surface to be cleaned, the soil loading, and the type and method of application.

Depending on the nature of the cosmetic product these could be applied a number of ways such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure assessment

6.1.1. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and Warehouse workers	5	None	Incidental Exposure only
Plant operators			
Mixer	5	4 hr/day	2 days/year
Drum handling	5	4 hr/day	2 days/year
Drum cleaning/washing	10	4 hr/day	2 days/year
Maintenance	5	4 hr/day	2 days/year
Quality control worker	2	0.5 hr/day	2 days/year
Packager	10	4 hr/day	2 days/year
End users (professionals)	> 1000	1-8	200

Exposure Details

Details on customer blending operations, worker exposure and life cycle of the notified chemical are not available. The number and category of workers will vary depending on the nature of the customers' business. However, it is anticipated that typical practices by cosmetic and consumer product manufacturers will include the use of adequate local ventilation, appropriate PPE, enclosed mixing vessel and filling areas as well as a high degree of process automation to protect workers.

At the IFF facility, transport and warehouse workers will be exposed to the fragrance oil (up to 10% notified chemical) only in the event of a spill due to an accident or leaking drum. Workers will wear protective overalls, hard hats, chemical resistant gloves and safety glasses.

At customer facilities (cosmetic and consumer product manufacturers), exposure to the fragrance oil (up to 10% notified chemical) or products containing the notified chemical (0.01-1%) is possible during handling of the drums, cleaning and maintenance of the equipment. Skin, inhalation and eye contact (due to splashing) are likely to be the main routes of exposure. The level of exposure would vary from site to site depending on the level of automation of the formulation process. The worst case dermal exposure is expected to be to workers directly handling the imported fragrance oil, and is estimated to be 0.01-0.1 mg/cm^2/day, based on EASE modelling (EASE) using reasonable worst case defaults for the exposure scenario 'manual addition of liquids' (European Commission, 2003) and assuming the notified chemical is present at a concentration of 10%. Therefore, assuming a surface area of 420 cm^2 (one hand) for a 70 kg worker and a 100% dermal absorption factor, systemic exposure is estimated to be 0.06-0.6 mg/kg bw/day. Exposure is likely to be minimised by good personal hygiene practices (eg. washing hands after any contact, before breaks and meals, etc) and use of industrial standard PPE.

According to EASE (1997) modelling of this work environment, in which it is assumed that non-dispersive use occurs in the presence of local exhaust ventilation, the estimated atmospheric concentration of notified chemical during handling of the imported fragrance oil (10% notified chemical) is 1-2 ppm (6.9-13.8 mg/m^3). Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/h, and 4 hour exposure, systemic exposure after inhalation is estimated to be 0.5-1.0 mg/kg bw/day. This estimate assumes that no respiratory protection is worn.

The worst-case total systemic exposure from the dermal and inhalation routes is therefore estimated as 0.56-1.6 mg/kg bw/day.

End use

Exposure to no more than 1% notified chemical could occur during final application of the cleaning/cosmetic products or during their addition to water if dilution is required. The main route of exposure is expected to be dermal, although ocular exposure to splashes is possible and inhalation of aerosols could occur where application is by spray. Although the level and route of exposure will vary depending on the method of application and work practices employed, exposure is considered to be low due to the low concentration of the notified chemical.

6.1.2. Public exposure

End-use products are designed to be sold to consumers. The general public will be repeatedly exposed to low-levels of the notified chemical via a number of different consumer products (typical levels 0.01-1%).

Acute dermal exposure

Use of perfumery products (such as toilet waters) and deodorant products are expected to give the highest exposure because of the relatively high concentration of the products applied to the skin, and the "leave-on" nature of these product categories. The maximum dermal exposure is estimated as shown below using consumer exposure data from the most relevant sources. In all calculations the retention factor for these products is assumed to be 1.

	Perfumery products	*Deodorant products*
Data Source	Tozer[a]	COLIPA[b]

Quantity product applied (mg)	-	1700
Surface Area (cm^2)	-	200 (100 per axillae)
Exposure to product ($\mu g/cm^2$)	2210	8500
Concentration of notified chemical (%)	0.8	0.1
Exposure to notified chemical ($\mu g/cm^2$)	17.68	8.5

[a] Measured/modelled data presented in Tozer et al (2004)
[b] Measured data presented in COLIPA's document on Dermal Sensitisation Quantitative Risk Assessment (QRA) for Fragrance Ingredients (COLIPA, 2006)

Chronic dermal exposure
The worst-case long-term dermal exposure to the notified chemical can be estimated by assuming that the notified chemical is present in the maximum amount in all cosmetic products used by the consumer, and that there is 100% dermal absorption. The estimated skin surface residue to fragrances due to use of a number of cosmetic products is estimated as 2.547 mg/kg bw/day (from Cadby, 2002). Therefore based on a concentration of 10% notified chemical in the fragrance compound the long-term dermal exposure to the notified chemical is estimated as 0.255 mg/kg bw/day.

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

Since products containing the notified chemical are stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw low toxicity
Rabbit, skin irritation	moderately irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – Repeat Insult Patch Test	no evidence of sensitisation at 5% concentration
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 150 mg/ kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberration assay in human lymphocytes	genotoxic
Genotoxicity – in vivo mouse micronucleus test	non genotoxic

Acute toxicity
Based on tests in rats the notified chemical exhibits low acute toxicity via oral or dermal exposure.

Irritation and Sensitisation
The notified chemical was moderately irritating to skin when tested undiluted on rabbits, producing very slight to well-defined erythema with or without slight oedema in all animals throughout the first 72 hours after exposure. The notified chemical is slightly irritating to eyes when tested in rabbits, producing mild conjunctival swelling (3/3 animals), and moderate conjunctival irritation (3/3 animals). The irritancy effects to the respiratory system were not investigated. However, based on the volatility of the chemical and the irritancy effects to skin and eyes it is possible that the notified chemical may be irritating to the respiratory system in high concentrations.

In a murine local lymph node assay there was evidence of a proliferative response indicative of skin sensitisation to the notified chemical. An EC3 value of 11.1% was calculated, which is equivalent to a threshold dose of 2775 μg/cm^2 (based on the fact that 25 μL of test solution was added to 1 cm^2 of the skin, the test solution applied was estimated to be 25,000 μg/cm^2).

In a human repeat insult patch test conducted using a 5% solution of the notified chemical there were no reactions indicative of irritation or sensitisation observed in any of the 107 subjects. The NOEL (based on the maximum concentration tested) was determined to be 2755 μg/cm^2.

Repeat dose toxicity
The effect of repeated exposure to the notified chemical for 28 days was investigated in the rat at dose levels of 15, 150 and 1000 mg/kg/day. The majority of findings observed were confined to the high dose group and although considered treatment related were largely of limited toxicological significance within each parameter. A NOEL could not be determined due to the finding of increased liver weights and increased globulin concentrations for all male treated animals. However, a NOAEL was established as 150 mg/kg bw/day, based on the microscopic findings in the stomachs of animals treated at 1000 mg/kg/day, which were indicative of an irritant effect.

Genotoxicity
The notified chemical was not mutagenic to *E. Coli* or *S. Typhimurium*, but was clastogenic to human lymphocytes *in vitro* in the absence of metabolic activation. However, the notified chemical did not cause chromosomal aberrations in mouse erythrocytes *in vivo*, and so is not considered to be an *in vivo* genotoxin.

Based on the skin irritancy and skin sensitisation effects observed in the toxicity tests the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Although the notified chemical is classified as irritating to the skin and showed slight irritancy to the eyes, the risk of irritancy effects in reformulation workers would be reduced due to the limited exposure through use of engineering controls and personal protective equipment, and the concentration of notified chemical in the imported product (up to 10%).

The highest occupational exposure is expected to occur to workers directly handling the imported fragrance mixture (10% notified chemical) when it is added to the mixing vessel during formulation of the end-products. Based on EASE modelling the worst-case total systemic exposure (in the absence of PPE) is estimated as 0.56-1.6 mg/kg bw/day. A dermal NOAEL was not determined, however a NOAEL of 150 mg/kg bw/day was established in a 28-day oral study in the rat. The use of this NOAEL results in a margin of exposure (MOE) of 94-268. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-

species differences. The MOE is based on conservative assumptions (100% dermal absorption, no PPE use) and likely overestimates the risk. Since the workers are expected to be wearing PPE, and the dermal absorption is likely less than 100%, the risk to formulation workers is considered to be acceptable.

The risk of skin sensitisation during the formulation process exists, especially for the workers manually handling (weighing, transferring) the imported product typically containing up to 10% of the notified chemical. However, the risk should be limited by workplace controls such as automated processes, use of PPE, and workplace regulatory labelling requirements for products containing notified chemical over the concentration cut-off (≥ 1% for skin sensitisation).

Although workers in the beauty industry may be dermally exposed to the notified chemical, the risk of irritancy effects is expected to be low due to the low concentration of notified chemical in the cosmetic creams and lotions (< 0.1%). The risk of skin sensitisation exists when professional cleaners and beauticians/hairdressers use end products containing the notified chemical. This risk would be limited by the low concentration of the notified chemical in both the cleaning products and the cosmetic creams and lotions (< 0.1%), as well as by use of gloves by cleaners.

6.3.2. Public health

The public may come into contact with the notified chemical (< 1%) through the use of a range of cosmetic and consumer products.

Systemic Toxicity

The worst -case long-term dermal exposure to the notified chemical is estimated as 0.255 mg/kg bw/day. A dermal NOAEL was not determined, however a NOAEL of 150 mg/kg bw/day was established in a 28-day oral study in the rat. The use of this NOAEL results in a margin of exposure (MOE) of 588. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. The MOE is based on conservative assumptions (e.g. 100% dermal absorption) and likely overestimates the risk.

Therefore the risk to the public of systemic effects after the use of cosmetic products is considered to be minimal based on the known systemic toxicity of the notified chemical (non-genotoxic *in vivo*; MOE for chronic effects >100).

Local Toxicity

The public will be exposed to the chemical at a maximum concentration of 0.8%. At this concentration the notified chemical is unlikely to be a skin irritant and therefore the risk of local irritancy effects is considered to be low, however, the risk of sensitisation cannot be ruled out.

Quantitative risk assessment for dermal sensitisation has not yet been validated and there is currently debate over the details of this process. A recent IPCS workshop has concluded that 'the relative ability of a chemical to induce sensitisation is an intrinsic property of the chemical, and is determined by the amount of chemical per unit area required for the acquisition of skin sensitisation in a previously naïve individual' (IPCS, 2007). Therefore it is considered that, despite the lack of validation, and in the absence of other alternatives, a quantitative risk assessment can provide an indication of the risk to the public of developing sensitisation to cosmetic products (i.e. risk of sensitisation induction, not elicitation).

The typical levels of dermal exposure (as amount of chemical per unit area of the allergen on the skin) were estimated as 17.68 μg/cm^2 for the perfumery product, and 8.5 μg/cm^2 for the deodorant product. Based on the EC-3 value of 11.1% from interpretation of the LLNA study data, a threshold dose of 2775 μg/cm^2 was calculated. This was consistent with results obtained in a Human Repeat Insult Patch Test where the NOEL was determined to be 2755 μg/cm^2, based on the maximum concentration tested. These concentrations are for induction of sensitisation, not for elicitation.

The selection of safety factors for the risk assessment is a current area of uncertainty. In the calculations below the safety factors are based on those given in the COLIPA Quantitative Risk

Assessment document (COLIPA, 2006) and include an inter-individual factor (10); a matrix factor based on the similarity of the product and the experimental conditions (3.16); and a use factor based on the similarity of the real-life exposure to the experimental conditions (10 for deodorant and 3.16 for perfumery products). An inter-species factor is not included as the LLNA data was shown to be a good estimate for the human NOEL.

	Perfumery product	*Deodorant product*
Threshold dose from LLNA	2775 μg/cm^2	2775 μg/cm^2
Safety factor	100	300
Acceptable exposure level (AEL) (threshold dose/safety factor)	27.75 μg/cm^2	9.25 μg/cm^2
Predicted maximum consumer exposure to notified chemical (CEL)	17.68 μg/cm^2	8.5 μg/cm^2
Risk Assessment	Acceptable (AEL > CEL)	Acceptable (AEL > CEL)

Based on these calculations the risk to the public is likely to be acceptable for the use of perfumery and deodorant products at the concentrations given by the notifier. Although the calculations are not shown here the risk to the public of sensitisation induction was also found to be acceptable for the other cosmetic products at the concentrations indicated by the notifier.

To determine the acceptable level of the notified chemical in cosmetic products the Acceptable Exposure Levels are divided by the estimated Consumer Exposure Level of the products. The calculations for the perfumery products and deodorant products are shown below.

	Perfumery product	*Deodorant product*
Acceptable exposure level (AEL)	27.75 μg/cm^2	9.25 μg/cm^2
Predicted maximum consumer exposure to product (CEL_{prod})	2210 μg/cm^2	8500 μg/cm^2
Concentration cut-off for acceptable sensitisation risk (AEL/CEL_{prod})x100	≤ 1%	≤ 0.1%

The calculated concentration cut-offs for all the other product types indicated by the notifier were greater than or equal to 1%. For rinse-off products, such as shampoos and household products, these values were much greater than the concentrations proposed by the notifier. Therefore a general concentration cut-off of ≤ 1% for all leave-on cosmetic products, other than deodorants, is considered to be suitable. For cosmetic deodorants, a concentration cut-off of ≤ 0.1% is considered acceptable to reduce the risk of sensitisation. It should be noted however that these values have been determined based on a range of typical consumer exposure scenarios, and therefore the risk of sensitisation cannot be completely ruled out for atypical exposure scenarios.

The concentrations above are related to the induction of sensitisation, not elicitation. Once an individual is sensitised to the notified chemical the concentration required to elicit an allergic response is likely to be less. Therefore while the risk of sensitisation induction may be acceptable for the cosmetic products at the concentrations indicated, the risk of sensitisation elicitation can not be quantified and is expected to be related to lower exposures to the notified

chemical.

The risk of toxic effects from accidental ingestion of products containing the notified chemical is considered to be low due to the low acute oral toxicity and the low concentrations of the notified chemical in the products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is imported and stored in a warehouse prior to shipping to the customer for reformulation (fragrance oil) or to retail stores (pre-formulated consumer product). No release is anticipated at the notifier's storage facility and during distribution and transportation to customer sites, except in the event of an accident. In the event of a transport accident, the type and size (205 L steel drums) of the containers and the concentration of the notified chemical (< 10%) would limit the release to the environment. Accidental spills of the notified chemical will be contained and the spilled chemical adsorbed on an inert support and disposed of to landfill.

Reformulation of the fragrance oil into consumer products will be by the batch process where cleaning the blending equipment may result in the generation of waste waters containing the notified chemical. This equipment may include automated mixing tank and filling machines. The quantity of notified chemical remaining in this wash water may be up to 1% of the import volume (10 kg/year). The disposal route for these waste waters may include disposal to on-site waste water treatment plants and/or the sewer system. The quantity of notified chemical remaining in the emptied import containers (205 L steel drums) may be up to 1% of the import volume (10 kg/year). The disposal route for container rinsate may include on-site waste water treatment plants and/or the sewer system.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used in household, laundry, and personal cleaning and care products. In these applications, it is anticipated that the entire product is eventually washed into the sewer system. The majority of the imported notified chemical (> 97%) is therefore expected to be disposed of to sewers.

RELEASE OF CHEMICAL FROM DISPOSAL

It is anticipated that up to 1% of the notified chemical will be lost as residues in consumer containers, which are primarily sent to landfill or recycled.

7.1.2 Environmental fate

The notified chemical is highly volatile and this property is expected to dominate the environmental fate of this chemical in the environment. For example, an analysis with the SIMPLETREAT model (EA 2003) indicates that in sewage treatment plants 71% of the notified chemical is lost by volatilisation, 10% to degradation, 15% to sludge, and 4% to the effluent. As the notified chemical is readily biodegradable (76.4% in 28 days), the residue in the sludge is expected to degrade by abiotic and biotic processes to oxides of carbon and water. For the details of the biodegradation study please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

It is anticipated that essentially all of the notified chemical (> 99%) will be released into the sewer system from the wash-off of products containing the chemical in domestic applications and clean-up of formulation equipment. As the notified chemical is to be used domestically, it is anticipated that release will occur on 365 days per year across Australia. The Predicted Environmental Concentration arising from this domestic release pattern was modelled using the SIMPLETREAT approach given the high potential of the notified chemical to partition to air.

The details of the calculation are presented below:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	1000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP:		
(a) Volatilisation	71	%
(b) Degradation	10	%
(c) Partition to sludge	15	%
(d) Remain in effluent	4	%
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.03	µg/L
PEC - Ocean:	0.003	µg/L

7.2. Environmental effects assessment

The notified chemical was shown to have a limited potential to inhibit microbial activity (EC50 (microbial respiration) = 1110 mg/L, Section C.2.1), but otherwise no eco-toxicity test results were submitted with this notification. The aquatic eco-toxicity for this chemical was therefore modelled using the EPIWIN suite of models. The modelling inputs included such relevant experimental data as were supplied with this notification. The results of this analysis are summarised below:

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h) 3.2 mg/L	Toxic
Daphnia Toxicity	LC50 (48 h) 1.1 mg/L	Toxic
Algal Toxicity	EC50 (96 h) 0.5 mg/L	Very toxic

These modelling results indicate that the notified chemical is potentially toxic to very toxic to aquatic life.

7.2.1 Predicted No-Effect Concentration

The Predicted No-Effect Concentration has been calculated from the algal toxicity of the notified chemical. As all of the toxicity data have been derived from modelling, the maximum assessment factor of 1000 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
	0.5	mg/L
Assessment Factor	1000	
Mitigation Factor	1.00	
PNEC:	0.5	µg/L

7.3. Environmental risk assessment

Based on the above PEC and PNEC values, the following Risk Quotient (Q) has been calculated:

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.03	0.5	**0.06**
Q - Ocean:	0.003	0.5	**0.01**

The mitigated Risk Quotients are much less than 1 for both the river and ocean disposal scenarios. Therefore, the notified chemical is not expected to pose an unacceptable risk to the aquatic environment based on the current use pattern and at the current import volume.

8. CONCLUSIONS – SUMMARY OF RISK ASSESSMENT FOR THE ENVIRONMENT AND HUMAN HEALTH

8.1. 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:

Risk phrases:

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

Safety phrases:

- S24 Avoid contact with skin
- S36 Wear suitable protective clothing
- S37 Wear suitable gloves

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.

	Hazard category	***Hazard statement***
Skin irritation	3	Mild irritant
Skin sensitisation	1	May cause an allergic skin reaction

8.2. 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.

8.3. Human health risk assessment

8.3.1. Occupational health and safety

There is a risk to workers of skin sensitisation after handling products containing the notified chemical. However, under the conditions of the occupational settings described (including the described use of any controls and personal protective equipment) the risk to workers is considered to be acceptable.

8.3.2. Public health

When used in the proposed manner the risk to the public is considered to be acceptable only when:

- used in leave-on cosmetic products, other than deodorants, at concentrations ≤ 1%; or
- used in cosmetic deodorants at concentrations ≤ 0.1%.

9. MATERIAL SAFETY DATA SHEET

The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS and is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

10. RECOMMENDATIONS

REGULATORY CONTROLS

Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:

Risk phrases:

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

Safety phrases:

- S24 Avoid contact with skin
- S37 Wear suitable gloves

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥ 20%: R38, R43
  - ≥ 1%: R43

- The National Drugs and Poisons Standing Committee (NDPSC) should consider the notified chemical for listing on the SUSDP so that the notified chemical is scheduled if at concentrations > 0.1% in deodorants, and > 1% in all other leave-on cosmetic products.

Health Surveillance

- As the notified chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Automation of formulation processes, especially transferring of the fragrance oils containing the notified chemical
  - Appropriate ventilation systems
  - Appropriate controls to avoid spillages

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Avoid contact with skin
  - Avoid contact with eyes

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Protective gloves
  - Protective clothing
  - Safety glasses
  - Respiratory protection where adequate ventilation is not present

  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 *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.

Public Health

- The following measures should be taken by the formulators to minimise public exposure to the notified chemical:
  - The notified chemical should not be used such that the level in the finished leave-on cosmetic products, other than deodorants exceeds 1%;
  - The notified chemical should not be used such that the level in the finished cosmetic deodorants exceeds 0.1%.

Disposal

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

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

11. REGULATORY OBLIGATIONS

Secondary Notification

This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical; or
  - the concentration of notified chemical in cosmetic products changes from the values provided in the notification; or

- the notified chemical is used in any consumer products not listed in the original notification; or
- the concentration of notified chemical in leave-on cosmetic products, other than deodorants, exceeds 1%; or
- the concentration of notified chemical in cosmetic deodorants exceeds 0.1%; or
- the notifier or introducer becomes aware of any adverse sensitisation effects from use of the notified chemical;

or

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from an odourant in alcoholic perfumery, cosmetics, toiletries, household products, soaps and detergents, or is likely to change significantly;
- the amount of chemical being introduced has increased from one tonne, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

APPENDIX A: PHYSICO-CHEMICAL PROPERTIES

Freezing Point < - 25ºC

METHOD OECD TG 102 Melting Point/Melting Range
EC Directive 84/449/EEC A.1 Melting/Freezing Temperature
Remarks No significant protocol deviations. GLP compliance
The test material continued to remain a liquid at -25 degrees C.
TEST FACILITY Huntingdon Life Sciences Limited (2006a)

Boiling Point 228ºC at 101.3 kPa

METHOD OECD TG 103 Boiling Point.
EC Directive 84/449/EEC A.2 Boiling Temperature
Remarks The boiling point was determined using the Siwoloboff method. No significant protocol deviations. GLP compliance.
Slight yellowing was noted at around the boiling temperature, indicating decomposition.
TEST FACILITY Huntingdon Life Sciences Limited (2006a)

Density 850 kg/m^3 at 20ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 84/449/EEC A.3 Relative Density.
Remarks The relative density was determined using a pycnometer and distilled water as the reference substance. No significant protocol deviations. GLP compliance.
TEST FACILITY Huntingdon Life Sciences Limited (2006a)

Vapour Pressure 1.52 kPa at 25ºC

METHOD OECD TG 104 Vapour Pressure.
EC Directive 84/449/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was determined by the static method (isoteniscope). The vapour pressure at 25ºC was interpolated from the temperature dependence of the vapour pressure of the notified chemical in the range 25-60ºC (2 replicates). According to Mensink et al (1995) the notified chemical is highly volatile.
TEST FACILITY Huntingdon Life Sciences Limited (2006a)

Water Solubility 0.055 g/L at 20ºC

METHOD OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The determination was carried out using the Flask method. Based on the preliminary test, 25 mg of the test material was combined with 30 mL distilled water. The concentration of the test material in the sample was determined by HPLC.
TEST FACILITY Huntingdon Life Sciences Limited (2006a)

Hydrolysis as a Function of pH The notified chemical is hydrolytically stable under neutral, acid and basic conditions at 25ºC.

METHOD OECD TG 111 Hydrolysis as a Function of pH.
EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.
Remarks The notified chemical was determined to have a half-life of > 1 year in aqueous solution at pH 4-9 and 25ºC based on preliminary tests carried out at 50ºC over 5 days. The concentration of the notified chemical was quantified by high-performance liquid chromatography on a reverse-phase column.
TEST FACILITY Huntingdon Life Sciences Limited (2006b)

Partition Coefficient (n-octanol/water) log P_{ow} = 4.4 at 20ºC

METHOD	OECD TG 117 Partition Coefficient-HPLC Method. EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks	Using 6 reference compounds with known K_{ow} values and an internal standard (formamide), a solution of notified chemical was chromatographed on a reverse-phase column and exponential regression used to determine the Log P_{ow} of the test material. The retention time of the notified chemical was bracketed by those for the reference compounds, benzyl benzoate and triphenylamine.
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

Surface Tension 50 mN/m at 20°C

METHOD	OECD TG 115 Surface Tension of Aqueous Solutions. EC Directive 92/69/EEC A.5 Surface Tension.
Remarks	This determination was carried out using a torsion/tension balance and a procedure based on the OECD harmonised ring method. No significant protocol deviations. GLP compliance. The surface tension of the sample was measured at intervals and reported as the mean over the initial 30-minute period. The surface tension measurement was corrected by interpolation from the Harkins-Jordan tables. As the surface tension is less than 60 mN/m, the notified chemical is considered to be surface active.
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

Adsorption/Desorption log K_{oc} = 3.0 at 20°C

METHOD	OECD TG 121 Estimation of the Adsorption Coefficient (K_{oc}) on Soil and Sewage Sludge by High-Performance Liquid Chromatography (HPLC). EC Directive, Method C19
Remarks	The sorption behaviour of the test substance on soil was investigated using high-performance liquid chromatography on a cyano-propyl stationary phase. Six reference substances with known K_{oc}s and an internal standard (formamide) were used. The retention time of the notified chemical was bracketed by those for the reference substances, nitrobenzene and naphthalene.
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

Dissociation Constant Not conducted

Remarks	The notified chemical does not have any groups capable of ionisation in the pH range 4-9.

Flash Point 96ºC at 101.3 kPa

METHOD	EC Directive 84/449/EEC A.9 Flash Point (Liquids)
Remarks	The flash point was determined by duplicate measurements using the Pensky-Martens closed cup tester. No significant protocol deviations. GLP compliance.
TEST FACILITY	Huntingdon Life Sciences Limited (2006c)

Autoignition Temperature 262ºC

METHOD	92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	No significant protocol deviations. GLP compliance.
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

Explosive Properties Not expected to be explosive

METHOD	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Based on an assessment of the chemical structure and the oxygen balance using the following calculation, the explosivity of the notified chemical is predicted to be negative.

	Oxygen balance = [-1600(2X +Y/2-Z)]/MW = -295 where X = number of carbon atoms, Y = number of hydrogen atoms, Z = number of oxygen atoms and MW = the molecular weight. (Lothrop and Handrich, 1949)
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

Oxidizing Properties	Not expected to be oxidising
METHOD	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	From an examination of the chemical structure it was noted that the notified chemical contained an oxygen atom, but that this was only chemically bonded to carbon. Consequently, the notified chemical would not be expected to possess oxidising properties.
TEST FACILITY	Huntingdon Life Sciences Limited (2006a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 2004/73/EEC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/CD (Crl:CD BR)
Vehicle	Corn Oil
Remarks - Method	No significant protocol deviations. GLP compliance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 female	300	0
2	3 female	300	0
3	3 female	2000	0
4	3 female	2000	0

LD50	> 2000 mg/kg bw
Signs of Toxicity	All animals receiving 300 mg/kg were noted with loose faeces 2 – 3 hours post dosing, resolving by day 2. All animals receiving 2000 mg/kg were noted with piloerection 2-3 hours after dosing. This was accompanied with loose faeces in three animals, four hours post dose and hunched posture in one animal at approximately 4.5 hours post dose. These signs had resolved by Day 2. No other signs of ill health, behavioural change or reaction to treatment were observed.
Effects in Organs	Terminal autopsy revealed no abnormalities
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Huntingdon Life Sciences (2006d)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 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 BR)
Vehicle	None. Test substance administered as supplied
Type of dressing	Occlusive
Remarks - Method	No significant protocol deviations. GLP compliance.

RESULTS

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

LD50	> 2000 mg/kg
Signs of Toxicity - Local	Well defined erythema was apparent at the site of application of the notified chemical in 2 male rats and very slight erythema was observed in

all females and the remaining males. Spotting and/or scabbing over a small proportion of the dose site were observed in three females. In addition, light brown staining was present over a small area of the dose site in the majority of the animals until termination.

Signs of Toxicity - Systemic	None
Effects in Organs	None

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

TEST FACILITY — Huntingdon Life Sciences (2006e)

B.3. Irritation – skin

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	Three
Vehicle	None. Test substance administered as supplied
Observation Period	Fifteen days
Type of Dressing	Semi-occlusive.
Remarks - Method	The test animals were obtained from two different commercial breeders. However this protocol deviation is not expected to affect the integrity of the study. No other significant protocol deviations. GLP compliance.

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	2.0	2.0	2	< 15 days	0
Oedema	1.7	1.0	0.3	2	< 15 days	0

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

Remarks - Results — Very slight to well-defined erythema with or without slight oedema was observed in all animals throughout the first 72 hours after exposure. These skin reactions had resolved by day 8 in one animal, and by day 15 in two animals. Exfoliation was apparent in two animals on Day 8 and in all animals on Day 15. Clear staining of the test site was observed in all animals, and had cleared by Day 15. This staining was not considered to interfere with the assessment of irritation.

CONCLUSION — The notified chemical is moderately irritating to the skin.

TEST FACILITY — Huntingdon Life Sciences (2006f)

B.4. Irritation – eye

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	Three
Observation Period	3 days
Remarks - Method	No significant protocol deviations. GLP compliance.

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	0.7	0.7	0.7	3	< 72 hours	0
Conjunctiva: chemosis	0	0	0.3	1	< 48 hours	0
Conjunctiva: discharge	0	0	0	2	< 24 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results: Instillation of the test substance gave rise to a slight or moderate initial pain response; local anaesthesia was employed for the last animal.

Crimson (2/3 animals) or beefy-red (1/3 animals) conjunctival appearance was observed 1 hour after instillation. Injection of the conjunctival blood vessels was observed in all animals at both 24 hours and 48 hours after instillation. Very slight chemosis with very light or slight discharge was observed in all animals 1 hour after instillation; in one animal the chemosis persisted for 24 hours.

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

TEST FACILITY: Huntingdon Life Sciences (2007a)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 429 Skin Sensitization: Local Lymph Node Assay.
EC Directive 2004/73/EEC B.42 Skin Sensitization: Local Lymph Node Assay.

Species/Strain: Mouse/ CBA/Ca

Vehicle: Acetone/olive oil 4:1 v/v

Remarks - Method: No significant protocol deviations. GLP compliance.
In a preliminary study using the dose levels 100%, 50% and 25% v/v it was found that 25% v/v was the most suitable high dose level for the main study.
The dpm count was determined individually for each animal and then the mean value for the five animals in each group was determined.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	293.25	-
5	395.45	1.3
10	747.60	2.5
25	2673.55	9.1
Positive Control		
25	3224.65	11.0

Remarks - Results: There were no deaths during the study. A loss of bodyweight was recorded for one female dosed at 10%. All remaining animals gained weight during the study.
Partially closed eyelids were noted in animals dosed at 10 or 25%,

	resolving completely by Day 3 or 4. No signs of irritation were seen over the dosed area during the study. As the stimulation index was above 3 for the animals dosed at 25% the notified chemical is considered to be a potential skin sensitiser. The EC3 value of the notified chemical was calculated as 11.1%. This is equivalent to a threshold dose of 2775 μg/cm^2. This calculation was done using the fact that the LLNA was performed by applying 25 μL of test solution to < 1 cm^2 of the mouse's ear, therefore, the concentration of test solution applied to the mouse ear was estimated to be 25 000 μg/cm^2 (assumed that 1mL = 1 g). The stimulation index of the positive control HCA (hexyl cinnamic aldehyde) was 11 which proved that the assay was reliable.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Huntingdon Life Sciences (2006g)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical
METHOD	Human Repeated Insult Patch Test/Adaptation of Draize Patch Test
Study Design	Induction Procedure: Repetitive application of sample (0.2 mL applied to a 3.63 cm^2 occlusive patch) to the same site on the skin for 24 hours on three days per week for approximately three weeks (total of nine applications). An alternative site was used if samples evoked irritation under conditions of the test. Rest Period: 14 days Challenge Procedure: Application of sample to a naïve site to test for reaction indicative of contact sensitisation. After 24 hours the challenge patches were removed and the test sites evaluated for dermal reactions, and then re-evaluated at 48 and 72 hours.
Study Group	112 subjects began the study. 5 subjects discontinued for reasons unrelated to the test material. A total of 107 subjects completed the study.
Vehicle	[75:25]Diethylphthalate: Alcohol SD39C
Remarks - Method	One subject missed the 48 hour challenge visit and one subject missed the 72 hour challenge visit. These subjects were evaluated at 96 hours post challenge patching.
RESULTS	
Remarks - Results	No reactions indicative of dermal irritation or sensitisation were observed. The No Observed Effect Level (NOEL) was therefore determined to be 2755 μg/cm^2 based on the amount of notified chemical applied and the size of the patch.
CONCLUSION	A human repeated insult patch test was conducted using the notified chemical diluted with [75:25] diethylphthalate:alcohol to 5% under occlusive dressing. The notified chemical was non-irritating and non-sensitizing under the conditions of the test in the 107 panelists tested.
TEST FACILITY	Clinical Research Laboratories, Inc (2006)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 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 / Crl:CD (SD)IGS
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	On Day 15 females in the high dose group received a dose which was 0.1 mL less than it should have been due to an error in the measurement of bodyweights. However, as the discrepancy in dose was small (≤10% of daily dose) and this only occurred on one day of the study, the dosing error is not considered to affect the validity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 male, 5 female	0	0
low dose	5 male, 5 female	15	0
mid dose	5 male, 5 female	150	0
high dose	5 male, 5 female	1000	0
control recovery	5 male, 5 female	0	0
high dose recovery	5 male, 5 female	1000	0

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

- Lower group mean bodyweight gains for males receiving 150 or 1000 mg/kg/day (resolution seen during recovery)
- Higher than control food intake for females receiving 1000 mg/kg/day (recovery was evident)
- Salivation associated with dosing, hair loss and body surface staining in both sexes at 1000 mg/kg/day
- Hair loss in females receiving 150 mg/kg/day, and in both sexes receiving 1000 mg/kg bw/day
- Higher activity levels in females at 1000 mg/kg/day (and to a lesser extent at 150 mg/kg/day). Some improvement seen during recovery
- Lower activity levels in males at 150 or 1000 mg/kg/day

Laboratory Findings – Clinical Chemistry

- Lower A/G ratios (due to lower globulin levels) in all animals at 1000 mg/kg/day (evident at recovery for females)
- Lower glucose for both sexes at 1000 mg/kg/day (evident at recovery for females)
- Lower sodium, chloride and phosphorous values for females at 1000 mg/kg/day
- Higher triglyceride, cholesterol and potassium values for females at 1000 mg/kg/day
- Higher triglyceride and lower phosphorus for females at 150 mg/kg/day

Laboratory Findings – Haematology

- Higher mean neutrophil and monocyte counts in females receiving 1000 mg/kg/day (recovery was evident)

Laboratory Findings – Urinalysis

- Abnormal colouration, ketone detection, pH changes, specific gravity changes and urinary volume changes for both sexes receiving 1000 mg/kg/day.
- At end of recovery males showed opposite effects on pH and SG, as well as lower protein levels.

Effects in Organs

- Higher adjusted liver weights for all treated male groups (dose related in degree) and for females at 1000

mg/kg/day

- Higher adjusted kidney weights in animals treated at 1000 mg/kg.day (recovery evident)
- Enlarged livers of all animals treated at 1000 mg/kg/day
- Depression and thickening of the epithelial aspect of the fore-stomach in females at 1000 mg/kg/day
- Microscopic changes in the stomach of animals treated at 1000 mg/kg/day indicative of an irritant effect: erosion of the glandular and non-glandular regions of the stomach (1 male); submucosal inflammation (1 male, 2 females); submucosal oedema and perakeratosis (1 male, 1 female); epithelial hyperplasia (3 females).
- Microscopic changes in the liver of animals treated at 1000 mg/kg/day: centrilobular hepatocyte hypertrophy (3 males, 3 females); slight periportal vacuolation (2 females)
- Hyaline droplets in kidneys of all males treated at 1000 mg/kg/day

Remarks – Results

The majority of the findings observed during the study were confined to the high dose group (1000 mg/kg/day) and although considered treatment related were of limited toxicological significance within in each parameter. In particular:

- There was no clear indication that the disturbances in motor activity were indicative of toxicity, since opposite trends were observed in males and females and no other functional differences were observed.
- The centrilobular hepatocyte hypertrophy and higher liver weights are considered to be adaptive in nature, and therefore not adverse
- The hepatic periportal vacuolation is usually attributable to fat accumulation and therefore indicative of toxicity, although minor and reversible. These findings could be associated with the slight changes in cholesterol and triglyceride levels observed in females at 1000 mg/kg/day
- Hyaline droplets in the kidneys are typically associated with a2u-glubulin accumulation and characteristic of light hydrocarbon nephropathy, which is a specific to the male rat. Therefore given the recovery observed and the irrelevance to man this is not considered to be an adverse effect
- The urine changes (including abnormal colour and presence of ketones) are considered to be a physiological response associated with the excretion of the test substance (a tertiary ketone) or a metabolite.
- The aetiology of the clinical chemistry disturbances is unknown. However as no corroborative findings indicate that the general health of the animals was affected and given the small magnitude of the differences the effects were not considered to be adverse.
- The extent of hair loss was observed to regress as the study progressed and is therefore not considered to be indicative of toxicity.

CONCLUSION

The presence of higher globulin levels and increased liver weights for all treated males does not allow the determination of a No Observed Effect Level (NOEL). The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study, based on the microscopic findings in the stomachs of animals treated at 1000 mg/kg/day.

TEST FACILITY	Huntingdon Life Sciences Ltd (2007)

B.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. Plate incorporation procedure (Test 1) / Pre incubation procedure (Test 2)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	S9 fraction from phenobarbital/5,6-benzoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5-5000 µg/plate b) Without metabolic activation: 5-5000 µg/plate
Vehicle	Dimethylsulphoxide
Remarks - Method	No significant protocol deviations. GLP compliance.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	≥ 5000	> 5000	negative
Test 2	-	150 (*S. typhimurium)* 5000 (*E. coli*)	> 5000	negative
Present				
Test 1	-	≥ 5000	> 5000	negative
Test 2	-	500 (*S. typhimurium)* 5000 (*E. coli*)	> 5000	negative

Remarks - Results: In the first test toxicity was only observed in strains TA1535 and TA1537. In the second test toxicity was observed in all strains.

No substantial increases in revertant colony numbers over control counts were obtained with any of the tester strains, without or with metabolic activation, when tested in either the plate incorporation or pre-incubation assays.

The positive control chemicals induced substantial increases in revertant colony numbers, confirming the sensitivity of the cultures and activity of the S9 mix.

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

TEST FACILITY: Huntingdon Life Sciences (2006h)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Dimethylsulphoxide
Remarks - Method	No significant protocol deviations. GLP compliance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	13.14, 26.27, 52.55, 105.09, 210.19, 420.38, 840.75, and 1681.5	3 hours	20 hours
Test 2	12.5, 25, 50*, 100*, 150*, 200, 250 and 300	3 hours	21 hours
Present			
Test 1	13.14, 26.27, 52.55, 105.09, 210.19, 420.38, 840.75, and 1681.5	3 hours	20 hours
Test 2	12.5, 25, 50*, 100, 150*, 200*, 250 and 300	3 hours	21 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	210.19	-	-
Test 2	-	150	-	positive
Present				
Test 1	-	210.19	-	-
Test 2	-	200	-	negative

Remarks - Results

Due to the steep toxic response seen in Test 1 no metaphase analysis was conducted, and a repeat test (Test 2) was conducted using lower concentrations.

In the absence of S9 mix the notified chemical caused dose related increases in the proportion of metaphase figures containing chromosomal aberrations. The values were outside historical controls for all dose levels examined, and were statistically significant at both 100 and 150 mg/mL when compared with the solvent control. In the presence of S9 mix the notified chemical caused no significant increases in the proportion of metaphase figures containing chromosomal aberrations.

All positive control compounds caused statistically significant increases in the proportion of aberrant cells, demonstrating the sensitivity of the test system and the efficacy of the S9 mix.

CONCLUSION

The notified chemical was clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Huntingdon Life Sciences (2006i)

B.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/CD1
Route of Administration: Oral – gavage
Vehicle: Corn oil
Remarks - Method: No significant protocol deviations. GLP compliance.
Animals were dosed on two consecutive occasions approximately 24 hours apart.

The high dose level was chosen following a preliminary toxicity test in which 4 animals (2 male, 2 female) were dosed at 2000 mg/kg bw/day on 2 consecutive days. This dose produced clinical signs of toxicity but was tolerated in both sexes. As there was no difference in toxicity between the sexes male animals only were used in the main test.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	7 male	0	24 hours after 2nd dose
II (low dose)	7 male	500	24 hours after 2nd dose

III (mid dose)	7 male	1000	24 hours after 2nd dose
IV (high dose)	7 male	2000	24 hours after 2nd dose
V (positive control, M)	5 male	12	24 hours after 1st dose

M=mitomycin C.

RESULTS

Doses Producing Toxicity	At 1000 mg/kg bw/day the only observed clinical sign was slightly under active behaviour observed in one animal 4 hours after the first dose. At 2000 mg/kg bw/day clinical signs included slight to severe under active behaviour, slow respiration, irregular respiration, hunched posture, flattened posture, prostrate posture, flattened gait, eyelids, partially closed, unsteady gait, ungroomed coat, absent righting reflex, uncoordinated gait, piloerection, reduced body temperature, and pallor skin colour. At 2000 mg/kg bw/day a statistically significant decrease in the proportion of immature erythrocytes was observed, indicating bone marrow cell toxicity at this dose.
Genotoxic Effects	The notified chemical did not cause any statistically significant increases in the number of micronucleated immature erythrocytes and individual and group mean values were within ranges determined from laboratory historical control data.
Remarks - Results	The clinical signs of toxicity indicate systemic exposure, and the decrease in the proportion of immature erythrocytes confirms that the target organ (bone marrow) was reached at 2000 mg/kg bw/day. The positive control caused a significant increase in the frequency of micronucleated immature erythrocytes, demonstrating the sensitivity of the test.

CONCLUSION

The notified chemical was not clastogenic under the conditions of this in vivo mouse micronucleus test.

TEST FACILITY

Huntingdon Life Sciences (2006j)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310 Ready Biodegradability: CO_2 in sealed vessels (Headspace Test)
Inoculum	Activated Sewage Sludge bacteria
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The total inorganic carbon content was determined by non-dispersive infra-red spectrophotometry.
Remarks - Method	The notified chemical and the reference substance (sodium benzoate) were added at nominal levels of 10 mg carbon/L to inoculated mineral salt medium aerated with CO_2-free air.

RESULTS

Test substance		*Reference Substance- Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	1.8	3	58.4
7	39.6	7	76.8
13	59.9	13	84.6
28	76.4	28	87

Remarks - Results	The graphs in the study report indicate 10% of the notified chemical was degraded by day 4, and 60% by day 14. Thus, the 10-day window specified in the test guideline appears to have (just) been met. The reference substance was degraded by 76.3% after 13 days in the presence of the notified chemical which confirmed that it does not inhibit the activity of the microbes.
CONCLUSION	The notified chemical is classified as readily biodegradable.
TEST FACILITY	Huntingdon Life Sciences Limited (2007c)

C.2. Ecotoxicological Investigations

C.2.1. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.4 Activated Sludge Respiration Inhibition Test.
Inoculum	A mixed population of activated sewage sludge micro-organisms.
Exposure Period	30 minutes
Concentration Range	Nominal: 60, 180, 540, 1620, and 4860 mg/L
Remarks – Method	An initial range-finding test of the notified chemical in the nominal concentration range 10-1000 mg/L indicated some inhibition of microbial activity at the highest concentration. A definitive test was carried out with nominal concentrations in the range 60-4860 mg/L. The reference inhibitor, 3,5-dichlorophenol (3-32 mg/L), was used as the positive control.

RESULTS	
EC50 (30 minutes)	1110 mg/L (95% confidence interval 407-4360 mg/L)
NOEC	
Remarks – Results	The inhibition of microbial respiration by the notified chemical was concentration dependent in the range-finding and definitive tests. The maximum inhibition observed was 66% at the highest nominal concentration of 4860 mg/L. The EC50 for the 3,5-dichlorophenol reference substance was 15.4 mg/L under the same conditions.
CONCLUSION	The EC50 (respiration inhibition) values for the notified chemical with activated sewage sludge have been determined as 1110 mg/L.
TEST FACILITY	Huntingdon Life Sciences Limited (2006k).

BIBLIOGRAPHY

Cadby, P.A., Troy, W.R., Vey, M.G.H. (2002) Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation. Regulatory Toxicology and Pharmacology, **36**: 246-252

Clinical Research Laboratories, Inc. (2006) Repeated Insult Patch Test (Study No. CRL104106-1, 13 November 2006) Clinical Research Laboratories Inc, Piscataway NJ, USA (Unpublished report provided by notifier)

COLIPA (2006) Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients – Technical Dossier (Revised 22 June 2006). QRA Expert Group convened by the COLIPA Toxicology Advisory Group and the Joint COLIPA/AISE/EFFA/IFRA Perfume Safety Group. http://www.ifraorg.org/Enclosures/News/Technical%20Dossier%20FINAL%20REVISED%202006%206%2022.pdf (Downloaded 3 May 2007)

Environment Australia (2003) Model and Guidance for Estimating Predicted Environmental Concentrations to Surface Water and Soil from Chemicals Released to the Environment Through a Sewage Treatment Plant. Chemical Assessment Section, Environment Australia, Canberra Australia.

FORS (Federal Office of Road Safety) (1998) Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), 6th Edition, Canberra, Australian Government Publishing Service

Huntingdon Life Sciences Limited (2006a) Methyl Decenone Physicochemical Properties (Study No. IFF0329/063215, 4 October 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006b) Methyl Decenone Abiotic Degradation: Hydrolysis as a Function of pH (preliminary Test) (Study No. IFF0308/063214, 20 October 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006c) Methyl Decenone Flash Point (Study No. IFF0319/053930, 4 October 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006d) Methyl Decenone Acute Oral Toxicity to the Rat (Acute Toxic Class Method) (Study No. IFF309/053988/AC, 6 January 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006e) Methyl Decenone Acute Dermal Toxicity to the Rat (Study No. IFF0310/063281/AC, 31 August 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006f) Methyl Decenone Skin Irritation to the Rabbit (Study No. IFF0311/063953, 4 December 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006g) Methyl Decenone Assessment of Skin Sensitization Potential Using the Local Lymph Node Assay in the Mouse (Study No. IFF0313/083989/LN, 9 January 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006h) Methyl Decenone Bacterial Reverse Mutation Test (Study No. IFF316/053789, 6 February 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006i) Methyl Decenone In Vitro Chromosome Aberration Test in Human Lymphocytes (Study No. IFF317/054048, 24 February 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006j) Methyl Decenone Mouse Micronucleus Test (Study No. IFF0326/062371, 29 June 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2006k) Methyl Decenone Activated Sludge-Respiration Inhibition Test (Study No. IFF0323/063433, 30 October 2006) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier).

Huntingdon Life Sciences Limited (2007a) Methyl Decenone Eye Irritation to the Rabbit (Study No. IFF0312/064188, 16 January 2007) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2007b) Methyl Decenone Toxicity Study by Oral Gavage Administration to CD Rats for 4 Weeks followed by a 2 Week Recovery Period (Study No. IFF0315/063789, 11 April 2007) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier)

Huntingdon Life Sciences Limited (2007c) Methyl Decenone Assessment of Ready Biodegradability: Sealed-Vessel Carbon Dioxide Evolution Test (Study No. IFF0324/064061, 10 January 2007) Huntingdon Life Sciences Ltd, Cambridgeshire, England (Unpublished report provided by notifier).

IPCS (2007) General Conclusions and Recommendations of an IPCS International Workshop on Skin Sensitization in Chemical Risk Assessment, 17-18 October 2006, Berlin, Germany. http://www.who.int/ipcs/methods/harmonization/areas/sensitization_summary.pdf. Accessed 15 May 2007

Lothrop W.C. and Handrich G.R. (1949), The Relationship between Performance and Constitution of Pure Organic Explosive Compounds, Chemical Reviews, 44 pp. 419-445.

Mensink BJWG, Montforts M, Wijkhuizen-Maslankiewicz L, Tibosch H and Linders JBHJ (1995) Manual for summarising and evaluating the environmental aspects of pesticides. National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands. Report No. 679101022.

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

SCCNFP (2001) Memorandum on the SCCNFP Opinion concerning Fragrance Allergy in Consumers adopted by the SCCNFP during the 16th Plenary Meeting of 13 March 2001.

SCCP (2006) The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 6th Revision. Adopted by the SCCP during the 10th plenary meeting of 19 December 2006.

Tozer, S.A., O'Keefe, L., Cowan-Ellsberry, C.E. and Rich K. (2004) Use of probabilistic analysis in the refinement of exposure date for hydroalcoholic perfume products. Toxicology **202**(1-2), 123-124.

United Nations (2003) Globally Harmonised System of Classification and Labelling of Chemicals (GHS). United Nations Economic Commission for Europe (UN/ECE), New York and Geneva.