File No: LTD/1479

January 2011

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Aldolone

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 Sustainability, Environment, Water, Population and Communities.

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 Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

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)
Firmenich Limited (ABN 86 002 964 794)
73 Kenneth Road,
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, method of detection and determination, and degree of purity.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for: Density, Vapour pressure, Hydrolysis as a function of pH, Adsorption/desorption, Particle size, Flammability and Explosive properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
LVC.

NOTIFICATION IN OTHER COUNTRIES
Switzerland, Canada, USA, EU, Philippines, and China.

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
ALDOLONE

3. COMPOSITION

DEGREE OF PURITY > 90%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% by weight)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: White to pale yellow solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	35°C	Measured
Boiling Point	306°C at 100.5 kPa	Measured
Density	Not determined	Crystalline solid
Vapour Pressure	1.40×10^{-5} kPa at 25°C	Estimated using MPBPVP (v1.43) (US

		EPA, 2009)
Water Solubility	2.35 g/L at 20°C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemical does not contain any readily hydrolysable functionality and is therefore expected to be hydrolytically stable
Partition Coefficient (n-octanol/water)	log K_{OW} = 2.80 at 21°C	Measured
Adsorption/Desorption	log K_{OC} = 1.91 – 2.78	Estimated using KOCWIN (v2.00) (US EPA, 2009)
Dissociation Constant	Not determined	The notified chemical does not contain dissociable functionality
Particle Size	Not determined	The substance is marketed or used in a non solid or granular form.
Flash Point	147ºC at 101 kPa	Measured
Flammability	Not determined	As the molecular structure of Aldolone does not contain groups that indicate potential reactivity with water or pyrophoric properties and handling of the substance indicates that this is the case.
Autoignition Temperature	402 ± 5 ºC	Measured
Explosive Properties	Not determined	The notified chemical is not expected to be explosive based on its structure.

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
The notified chemical has a good stability at standard temperature.

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However the data above do not address all Dangerous Goods endpoints. Therefore consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical is not manufactured in Australia. It will be imported as a small component (maximum 0.1%) of compounded fragrances.

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

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

PORT OF ENTRY
Sydney, by wharf or airport

IDENTITY OF MANUFACTURER/RECIPIENTS
The fragrance preparations containing the notified chemical will be imported by Firmenich Ltd and will be reformulated locally. The fragrance preparations containing the notified chemical will initially be stored in the notifier's site and then distributed to customers (manufacturers of cosmetics, toiletries and household products).
TRANSPORTATION AND PACKAGING
The fragrance preparations containing the notified chemical at a maximum of 0.1%, will be imported and

distributed in tightly closed lacquered drums, typically of 180 kg size, but also in 5, 10, 25, 50 or 100 kg packages. The fragrance preparations will be transported by road from the wharf or airport of entry to the Firmenich Ltd warehouse for storage and then directly to the clients by road. Final consumer products will be transported to retails stores for distribution and will be sold in a variety of small package sizes, typical of consumer-sized containers.

USE
The notified chemical will be used as a fragrance ingredient in a variety of cosmetic and domestic products. In final finished products, the concentration of the notified chemical will be at a maximum of 0.1% in fine perfumes and a maximum of 0.0025% in other cosmetic and domestic products.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia and will be imported as a small component (maximum of 0.1%) of compounded fragrances. The fragrance preparations containing the notified chemical will be reformulated in Australia and will be used to manufacture perfume cosmetics, household cleaning and detergent products.

The reformulation process mainly involves a blending operation which will be highly automated and will occur in a fully enclosed environment, followed by automatic filling in containers of various sizes. The final consumer products containing the notified chemical up to 0.1%will be distributed to retail outlets, displayed and sold to the public.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	4	Unknown	unknown
Mixer	5	4	2
Drum handling	5	4	2
Drum cleaning	8	4	2
Maintenance	5	4	2
Quality control	1	0.5	1
Packaging	10	4	2
Salon workers	100	1	300

EXPOSURE DETAILS
The major occupational exposure to the notified chemical will be at the reformulation plants where the imported containers of fragrance mixtures containing the notified chemical are opened and used. Workers may be exposed to fragrances containing the notified chemical during handling of the drums, weighing and charging them to the blending vessel, mixing in open vessels and also during cleaning operations, production line, and sampling or analysis tasks. Exposure via all three routes (dermal, ocular and inhalation) is anticipated to be minimal and irregular. The number and category of workers will depend on the nature of the customers business.

Reformulation is usually done in fully automated systems, however some facilities may not be fully automated. Hazardous components of the products mixed together as well as the size of the batches usually necessitate the use of closed lines, local exhaust ventilation, where vapours or aerosols are produced, and automated packing lines.

All workers handling perfume preparations containing the notified chemical and involved in open mixing operations will wear suitable gloves, eye and face protection and protective clothing. If open vessels are used for mixing, adequate ventilation should be provided to remove aerosols that may arise during the process. It is very unlikely that the product containing the notified chemical at 0.1% will be added to the mixing vessel

manually.

Workers in hair and beauty salons will experience extensive dermal exposure during application of products containing the notified chemical at up to 0.0025% by hand. Such professionals may use some personal protective equipment to minimise repeated exposure, and good hygiene practices are expected to be in place. Exposure of such workers is expected to be of a similar or higher level than that experienced by consumers using products containing the notified chemical.

Overall, the exposure of workers to the notified chemical is expected to be low.

6.1.2. Public exposure

During import, transport, storage, reformulation of fragrance compositions containing the notified chemical at up to 0.1% concentration, exposure of the general public will be limited, except in the event of an accidental spill.

Consumer products containing the notified chemical (fine fragrance, cosmetics and homecare products) will be sold in the public domain, consequently there is potential for widespread public exposure to very low concentration. Exposure will be mainly via dermal route.

Exposure to the notified chemical is considered minimal given the very low concentration of notified chemical in the final consumer products.

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
Rabbit, skin irritation	irritant
Rabbit, eye irritation	slightly irritating with reversible effect
Guinea pig, skin sensitisation –adjuvant test.	not a skin sensitiser
Mutagenicity – bacterial reverse mutation	non mutagenic
Human Repeat Insult Patch Test (at 1% in Diethyl phthalate)	non sensitizer
Human Repeat Insult Patch Test (at 10% in Diethyl phthalate)	non sensitizer

Toxicokinetics, metabolism and distribution.
Given the notified chemical has a low molecular weight and relatively high water solubility (>2.35 g/L) dermal absorption may occur. However, this is expected to be limited based on the partition coefficient (log P_{ow} estimated to be 2.80).

Acute toxicity.
The notified chemical is of low acute toxicity *via* the oral route.

No acute dermal or inhalation toxicity study was conducted using the notified chemical. Inhalation toxicity is expected to be low as the notified chemical has a very low vapour pressure (1.40×10^{-5} kPa).

Irritation and Sensitisation.
The notified chemical was irritating to the skin and slightly irritating to the eyes of rabbits.

The notified chemical is not a skin sensitiser in guinea pigs. It is also not a skin sensitiser in 104 subjects in a human insult patch test using a 1% concentration in diethyl phthalate and in 108 subjects in a repeated insult patch test using 10% concentration in Diethyl Phthalate (Modified Draize).

Mutagenicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study.

Health hazard classification
Based on the skin irritation test, the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase:

R38: Irritating to skin

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
The primary risk associated with the use of the notified chemical is its potential to cause skin irritation. However, as the notified chemical will be imported at the maximum finished concentration of 0.1%, the risk of skin irritation is not expected to be present at such low concentration.

Furthermore, the use of highly automated and fully enclosed blending processes and together with the automatic filling and low concentration of the notified chemical present and the use of personal protective equipment (PPE), will ensure minimal occupational risk posed by the notified chemical in these products to workers.

6.3.2. Public health
Members of the public will experience widespread and frequent exposure to the notified chemical through daily use of cosmetic and domestic products at a maximum concentration of 0.1%. At this concentration, there is no risk of notified chemical causing skin irritation. No information is available on repeat dose toxicity of the notified chemical to assess its repeat dose effects. However, based on the low concentration of the notified chemical (maximum 0.1%) in products, repeat dose risks are expected to be low.

Overall, based on the available data, the notified chemical is not expected to pose unacceptable risk to public health at concentration up to 0.1% in cosmetic and domestic products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance preparations for local reformulation into a variety of consumer products (cosmetics, household products, fine fragrances). Losses during the blending processes at various sites throughout Australia are expected to be limited to traces of spills, formulation equipment cleaning and residues in empty packaging. Less than 0.1 % of the total annual import volume of notified chemical is expected to remain as residues in import containers. The empty containers will eventually be recycled or disposed of to landfill. At the end of the reformulation run the formulating equipment and packing equipment are washed and it is anticipated that the washings will be included in the next batch.

Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
Most of the notified chemical will be incorporated as a fragrance additive into a variety of consumer products for dispersed use throughout Australia. Whilst there will be some releases of this moderately volatile fragrance chemical to the atmosphere, the majority of the imported quantity of notified chemical is expected to be released to sewer in domestic situations.

RELEASE OF CHEMICAL FROM DISPOSAL
Expired wastes and residue of the notified chemical in empty containers (<1%) are likely either to share the fate of the container and be disposed of to landfill, or to be washed to the sewer when containers are rinsed before recycling.

7.1.2 Environmental fate

The notified chemical is a moderately volatile compound and a fraction of the imported quantity of this chemical will partition to air, which is a functional requirement for fragrant products. The half-life of the notified chemical in air was calculated to be 2.24 h, based on reactions with hydroxyl radicals over a 12 hour day, and reaction with ozone is not expected (AOPWIN, v1.92; EPISuite, US EPA 2009). The notified chemical is therefore not expected to persist in the air compartment.

The major proportion of the imported quantity of notified chemical will enter the sewer system as a result of the use of this chemical as an odorant in domestic consumer products such as cosmetics and household products. The notified chemical did not satisfy the criteria for ready biodegradability, but the extent of biodegradation (44%) in the test indicates that biodegradation can be expected to occur in the environment, and to some extent during sewage treatment. Based on its low adsorption coefficient (log K_{OC} = 1.91–2.78), only limited partitioning to sludge is expected. Most of the notified chemical is expected to remain in the water phase, due to its high water solubility, and may be released from sewage treatment plants to receiving waters, where it will disperse and degrade. It has low potential to bioaccumulate, based on its low octanol/water partition coefficient (log K_{OW} = 2.8) and its low bioconcentration factor (log BCF = 1.51) predicted by a regression-based method based on the measured partition coefficient (BCFBAF v3.00; US EPA, 2009). A small proportion of notified chemical may be applied to land when effluent is used for irrigation or sewage sludge is used for soil remediation. Notified chemical residues in landfill, soil and sludge are likely to be mobile, and is expected to degrade biotically or abiotically to form water and oxides of carbon.

For the details of the environmental fate studies, refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

A Predicted Environmental Concentration (PEC) has been calculated assuming a worst case in which 100% of the annual imported quantity of notified chemical will be released to sewer nationwide and that no removal of the notified chemical will occur at sewage treatment plants.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	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)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.65	µg/L
PEC - Ocean:	0.06	µg/L

The removal of up to 43% of the notified chemical from influent during sewage treatment plant (STP) processes is predicted based on 39% degradation and 4% partitioning to sludge (SimpleTreat; European Commission, 2003). However, for this worst case scenario it is assumed that all of the notified chemical is released to the environment as STP effluent. STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.647 µg/L may potentially result in a soil concentration of approximately 4.316 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 21.58 µg/kg and 43.16 µg/kg, respectively. However, given the inherent biodegradability of the notified chemical, these calculated values represent maximum concentrations only.

7.2. Environmental effects assessment

No ecotoxicity data were submitted. The acute toxicity for the notified chemical was estimated using the neutral organics structure-activity relationship (SAR) from the ECOSAR suite of models. The modelled estimates (ECOSAR (v1.00), neutral organics SAR; US EPA, 2009) for the acute and chronic endpoints of the notified chemical are tabulated below.

Endpoint	*Result*	*Assessment Conclusion*
Acute Toxicity		
Fish	96 h LC50 = 31.4 mg/L	Harmful to fish
Daphnia	48 h EC50 = 19.9 mg/L	Harmful to aquatic invertebrates
Algae	96 h EC50 = 13.4 mg/L	Harmful to algae
Chronic Toxicity		
Fish	30 d ChV‡ = 3.46 mg/L	Not harmful to fish
Daphnia	16 d ChV‡ = 2.63 mg/L	Not harmful to aquatic invertebrates
Algae	96 h ChV‡ = 5.85 mg/L	Not harmful to algae

‡ ChV (Chronic Value) = $(LOEC \times NOEC)^{½}$

Under the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS), the notified chemical is considered to be harmful to fish, daphnia and algae. Based on its acute toxicity to aquatic biota, the notified chemical is formally classified under the GHS as 'Acute Category 3; Harmful to aquatic life'. The notified chemical is not predicted to have long-term harmful effects to aquatic biota and therefore it is not classified for long term hazard.

7.2.1 Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the predicted chronic endpoint for the most sensitive species (daphnia 16 day ChV = 2.63 mg/L) and an assessment factor of 50. A more conservative assessment factor of 50 is appropriate in this case as although chronic endpoints (ChV = $(LOEC \times NOEC)^{½}$) for three trophic levels were reliably estimated by the neutral organics SAR (ECOSAR (v1.00); US EPA, 2009), the chronic endpoints are not NOECs.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
ChV (Algae)	2.63	mg/L
Assessment Factor	50	
PNEC:	52.6	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:	0.65	52.6	0.012
Q - Ocean:	0.06	52.6	0.001

The majority of the notified chemical will be disposed of to the sewer where it is expected to slowly degrade during sewage treatment plant processes. The notified chemical has a low potential for bioaccumulation and is unlikely to persist in surface waters if released in treated effluent. The risk quotient (PEC/PNEC) for the conservative worst case scenario of unmitigated release of the notified chemical to surface waters in treated effluents is well below 1 for both riverine and oceanic discharge scenarios. Therefore, at the maximum importation volume, the notified chemical is not expected to pose a risk to the environment when used as described.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the data provided, the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)], with the following risk phrase:

Xi; R38 Irritating to skin

and

As a comparison only, the classification of the 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***
Irritating to skin	2	Causes skin irritation
Aquatic Environment	Acute Category 3	Harmful to aquatic life

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to the health of workers.

When used in the proposed manner, the notified chemical is not considered to pose an unacceptable risk to public health.

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not expected to pose a risk to the environment.

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- Safe Work Australia, should consider the following hazard classification for the notified chemical:
  - R38 Irritating to skin
- Use the risk phrase R38 for products/mixtures containing the notified chemical ≥20%

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 and used:
  - Avoid contact with skin

  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* [NOHSC:1008(2004)] 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 to landfill.

Emergency procedures

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

Regulatory Obligations

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 of NICNAS 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;

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of fine perfumes and other cosmetic and domestic products at 0.1%, or is likely to change significantly;
  - 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.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the notified chemical and products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 35ºC

Method	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Differential scanning calorimetry (DSC)
Test Facility	Safepharm Laboratories (1998a)

Boiling Point 306ºC at 100.5 kPa

Method	EC Directive 92/69/EEC A.2 Boiling Temperature.
Test Facility	Safepharm Laboratories (1998a)

Vapour Pressure 0.153×10^{-3} kPa at 25 ºC

Method	EPISuite-BioWIN
Remarks	Calculated
Test Facility	EPISuite-BioWIN

Water Solubility 2.35 g/L at 20 ± 0.5ºC

Method	EC Directive 92/69/EEC A.6 Water Solubility. Flask Method. In triplicate, test material (~1 g) was added to double distilled water (100 mL) and shaken at ~30°C for 24 to 72 hours. After standing for 24 h at 20°C, the test samples were filtered and measured for pH. The concentrations of the test substance in the sample solutions were determined by HPLC (UV).
Remarks	The pH was measured to be 4.5, 6.3 and 5.0 depending on whether the test solutions were shaken at 30°C for 24, 48 or 72 hours, respectively.
Test Facility	Safepharm Laboratories (1998a)

Partition Coefficient (n-octanol/water) $\log K_{OW} = 2.80$ at 21 ± 0.5°C

Method	EC Directive 92/69/EEC A.8 Partition Coefficient. Shake Flask Method. A stock solution of the test material in octanol-saturated water was combined with water-saturated octanol (six replicates). The combined phases were shaken for 5 mins and allowed to separate. The concentration of the test material in each phase was determined by HPLC (UV).
Remarks	The partition coefficient was calculated from the ratio of the concentrations of the test substance in each phase.
Test Facility	Safepharm Laboratories (1998a)

Flash Point 147ºC at 101 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	The determination was carried out using the closed cup equilibrium method.
Test Facility	Safepharm Laboratories (1998b)

Autoignition Temperature 402 ± 5 ºC

Method	Firmenich in house method, AIT instrument
Remarks	According to the norm DIN 51794 (ASTM2155)
Test Facility	Firmenich in house method

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (>90%)
METHOD	OECD TG 420 Acute Oral Toxicity: Fixed Dose Method. EC Directive 92/69/EEC B.1 Acute Toxicity (Oral) Commission Directive.
Species/Strain	Rat/Sprague-Dawley CD
Vehicle	Arachis oil BP
Remarks - Method	Single dose, oral gavage

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	Common signs of systemic toxicity noted during the study were hunched posture, ataxia, lethargy, decreased respiratory rate, laboured respiration and loss of righting reflex with incidents or isolated incidents of pilo-erction, prostration, splayed gait and increased lacrimation. Surviving animals recovered three to four days after dosing.
Effects in Organs	No abnormalities were noted at necropsy.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories (1998d)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical (>90%)
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	3
Vehicle	Distilled water
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	0.5 g of the notified chemical, diluted in 0.6 ml of distilled water was introduced under cotton gauze patch and placed in position on the shorn skin.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period (14-day)*
	1	2	3			
Erythema/Eschar	1.3	2.0*	2.0*	2.0*	72h	0
Oedema	0.3	1.3	2.0*	2.0*	72h	0

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

Remarks - Results	Well-defined erythma was noted at all treated skin sites one hour after

patch removal and at the 24-hour observation. Well defined erythma was noted at two treated skin sites with very slight erythma at the remaining treated skin site at the 48 and 72-hour observations.
Slight oedema was noted at two treated skin sites with very slight oedema at the remaining treated skin one hour after patch removal and at the 24-hour observation. Slight oedema was noted at one treated skin site with very slight oedema at one other treated skin site at the 48 and 72-hour observations.
Loss of skin elasticity and flexibility were noted at one treated skin site at the 48 and 72-hour observations. Moderate desquamation was noted at two treated skin sites with slight desquamation at the remaining treated skin site at the 7-day observation.
Treated skin sites appeared normal at the 14-day observation.
The test substance produced positive criteria in 2/3 rabbits and was classified as irritant to rabbit skin under EU labelling regulations.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY Safepharm Laboratories (1998e)

B.3. Irritation – eye

TEST SUBSTANCE Notified chemical (>90%)

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	3
Observation Period	72 hours
Remarks - Method	0.1 ml of the notified chemical was placed into the conjunctival sac of the right eye, formed by gently pulling the lower lid away from the eyeball.

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	0.3	0.3	0.3	1	24 hours	0
Conjunctiva: chemosis	0.3	0	0	1	24 hours	0
Conjunctiva: discharge						
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results Treated eyes appeared normal at the 48-hour observation.

CONCLUSION The notified chemical was slightly irritating to the eyes with reversible effect.

TEST FACILITY Safepharm Laboratories (1998f)

B.4. Skin sensitisation

TEST SUBSTANCE: Notified chemical (>90%)

METHOD: OECD TG 406 Skin Sensitisation - Magnusson & Kligman Maximisation.
EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson & Kligman Maximisation.

Species/Strain: Guinea pig/38 female albino Dunkin Hartley guinea pigs

PRELIMINARY STUDY: Maximum Non-irritating Concentration: 25% in arachis oil BP
intradermal: 1%, 5%, 10% and 25% in arachis oil BP
topical: 10%, 25%, 50% and 75% in arachis oil BP

MAIN STUDY

Number of Animals: Test Group: 20 Control Group: 10

INDUCTION PHASE: Induction Concentration:
intradermal: 5% in arachis oil BP
topical: 75% in arachis oil BP

Signs of Irritation: Intradermal induction: Very slight erythema was noted at the intradermal induction sites of 8 control group animals at the 24-h observation and in 4 control group animals at the 48-h. Well-defined or moderate to severe erythema was noted at the intradermal induction sites of all test group animals at the 24 and 48-h observation.
No signs of erythema or oedema were noted at the treatment sites of control group animals at the 1-24-h observation after topical induction.
Topical induction: Individual skin reactions observed at the topical induction sites of the test and control group animals.
Well defined erythma and very slight oedema were noted at the induction sites of all test group animals at the 1-hour observation with very slight to well defined erythma with or without very slight to slight oedema at the 24-hour observation. Bleeding from the injection sites was noted in six test group animals at the 1-hour observation.

CHALLENGE PHASE

1st challenge: topical: Challenge at 75% in arachis oil: 5/20 animals exhibited dermal responses

2nd challenge: topical: Challenge at 50% in arachis oil: 4/20 animals exhibited dermal responses.

Remarks - Method: Same animals were challenged at different sites with 75% and 50% concentration of the notified chemical and examined at 24 hours and 48 hours for sign of sensitisation.
Induction of the control group: Intradermal injections were administered using an identical procedure to that used for the test animals (50% formulation of arachis oil BP in Freund's Complete Adjuvant/distilled water).

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	75%	5/20	3/20
	50%	4/20	1/20
Vehicle Control Group	0%	0/10	0/10

Remarks - Results: No skin reactions were noted at the challenge sites of vehicle control group animals at the 24-48-h observation. There were 25% and 20% animals showing positive skin reactions after 24 hours and 15% and 5% after 48 hours for challenge concentration of 75% and 50% respectively.
No concurrent positive control was done for this study. However, a historical positive control test has been done in November 1996 with a positive control material 2-Mercaptobenzothiazole and challenge concentration of 25 and 50% in acetone showing 90% (9/10 animals) incidence of sensitisation.

CONCLUSION	A response of at least 30% is expected for mild/moderate sensitisers according to OECD TG 406 for an adjuvant test. As the positive response rate is below this level, the notified chemical is not considered to be a skin sensitiser.
TEST FACILITY	Safepharm Laboratories (1997)

B.5. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical (>90%)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Ames plate incorporation method and Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 and Echerichia Coli strain WP2uvrA$^-$.
Metabolic Activation System	Aroclor 1254 activated S9 fraction
Concentration Range in Main Test	a) with metabolic activation: 5-5000 µg/plate b) without metabolic activation: 15-5000 µg/plate
Vehicle	Sterile distillate water
Remarks - Method	Two independent mutation tests were performed. The dose range for the first experiment was determined in a preliminary toxicity assay.

RESULTS

Metabolic Activation	*Cytotoxicity in Preliminary Test*	*Test Substance Concentration (µg/plate) Resulting in: Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	1500	5000 (all strains)	Not indicated	Negative
Test 2	5000 (all strains)	1500 (TA100 strain)	Not indicated	Negative
Present				
Test 1	1500	5000 (all strains)	Not indicated	Negative
Test 2	-	5000 (all strains) 1500 (TA100 strain)	Not indicated	Negative

Remarks - Results	The test material caused a visible reduction in the growth of the bacterial lawn to Salmonella tester strain TA100 at 1500 µg/plate and all of the tester strains, both with or without S9-mix at 5000 µg/plate. Test material was tested up to the maximum recommended dose of 5000 µg/plate. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation. The vehicle (sterile distilled water) control plates gave counts of revertant colonies within the normal range. All positive control chemicals used in the test, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), 9-aminoacridine (9AA), 4-nitroquinoline-1-oxide (4NQO) without metabolic activation S9-Mix and 2-aminoanthracene (2AA), and Benzo(a)pyrene (BP) with S9-Mix, induced marked increases in the frequency of revertant colonies, both with and without metabolic activation.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1998c)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (1%)
METHOD	Occlusive human repeated insult patch test (HRIPT)
Study Design	Induction Procedure: 9 consecutive applications of the test substance Rest Period: 12-14 days Challenge Procedure: Challenge phase initiated during the sixth week of the study, with identical patches applied to sites previously unexposed to the study material. These patches were removed by subjects after 24 hours and the sites graded after additional 24 hours and 48 hours periods, i.e. , 48 and 72 hours after application. One hundred-seven subjects between the ages of 18 and 74 were involved and 104 subjects completed the study. To be considered a complete case, a subject must have nine applications and no less than eight subsequent readings during induction and one product application and two readings during challenge. Only completed cases were used to assess sensitisation.
Study Group	Individuals: 18 years of age or older free of any systemic or dermatologic disorder uniformly colored skin
Vehicle	DEP
RESULTS	
Remarks - Results	Under the conditions employed in this study, there was no evidence of sensitisation to the test substance.
CONCLUSION	A RIPT was conducted using test substance diluted with DEP to 1% under occlusive dressing. The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	TKL Research USA (1999)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (10%)
METHOD	Occlusive human repeated insult patch test (HRIPT)
Study Design	Induction Procedure: 9 consecutive applications of the test substance Rest Period: 10-14 days Challenge Procedure: Challenge phase initiated during the fifth week of the study, with identical patches applied to sites previously unexposed to the study material. These patches were removed by subjects after 24 hours and the sites graded after additional 24 hours and 48 hours periods, i.e., 48 and 72 hours after application. One hundred-eight subjects completed the study. To be considered a complete case, a subject must have nine applications and no less than eight subsequent readings during induction and one product application and two readings during challenge. Only completed cases were used to assess sensitisation. The notified chemical at 10% in DEP was applied.
Study Group	Individuals: 135 (104 females + 31 males) 18 to 70 years of age free of any systemic or dermatologic disorder
Vehicle	DEP

RESULTS	
Remarks - Results	Under the conditions employed in this study, there was no evidence of sensitisation to the test substance.
CONCLUSION	A RIPT was conducted using test substance diluted with DEP to 10% under occlusive dressing. The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	RCTS, Inc. USA (2000)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical (>90%)
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge from a domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The biological oxygen demand was determined by Camlab BOD consumption apparatus. Evolved carbon dioxide was absorbed using potassium hydroxide solution.
Remarks - Method	In accordance with the guidelines above, the oxygen consumption of inoculated medium containing the test substance (100 mg/L) in darkened enclosed culture vessels was measured over 28 days. A reference control (aniline, 100 mg/L) and a toxicity control (aniline and test substance, 100 mg/L each) were run in parallel. Biodegradation is expressed as the percentage oxygen uptake, corrected for the blank, of the theoretical oxygen demand (ThOD). Test conditions were: 21 ± 1°C, pH 7.3-11.0.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	13	7	56
14	29	14	62
28	44	28	65

Remarks - Results	The reference control achieved >60% degradation by Day 14, and therefore the test is considered valid for this criterion. Whilst the oxygen uptake of the inoculum blank did not exceed 60 mg O_2/L, it was not in the usual range of 20-30 mg O_2/L. Additionally, the pH measured over the duration of the study was outside the range 6-8.5. However these phenomena are not expected to affect the outcome of the test. The toxicity control achieved 39% degradation by Day 14 and, as this surpasses the pass level of 25%, the test material is considered non-inhibitory to the inoculum used in the study. The test substance achieved 44% degradations after 28 days and, as the pass levels of >60% were not reached, it is not considered to be readily biodegradable. Biodegradation above 20% may be regarded as evidence of inherent primary degradation.
CONCLUSION	The notified chemical is not readily biodegradable, but indicates inherent primary biodegradation.
TEST FACILITY	Safepharm Laboratories (1998g)

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