File No: LTD/1787

December 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

2(3*H*)-Benzofuranone, hexahydro-3,6-dimethyl-

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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 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.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This 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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

TABLE OF CONTENTS

SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1787	Firmenich Ltd	2(3*H*)-Benzofuranone, hexahydro-3,6-dimethyl-	No	≤1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Human health risk assessment

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable 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 considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation:
  - Local exhaust ventilation, if available.

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation:
  - Avoid skin and eye contact

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Impervious gloves, eye protection and protective clothing

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

- A copy of the (M)SDS should be easily accessible to employees.

Disposal

- Where reuse or recycling are unavailable or impracticable, dispose of the chemical in an environmentally sound manner in accordance with relevant Commonwealth, State, Territory and local government legislation.

Emergency procedures

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

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 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;
- the concentration of the notified chemical exceeds or is intended to exceed 1% in air freshener or 0.5% in cosmetic and other household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, 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.

(Material) Safety Data Sheet
The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
Firmenich Ltd (ABN: 86 002 964 794)
73 Kenneth Rd
Balgowlah NSW 2093

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: analytical data, degree of purity, and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: adsorption/desorption, dissociation constant, particle size, flammable limits, explosive properties, oxidising properties and reactivity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA, EU (EFSA)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Natactone

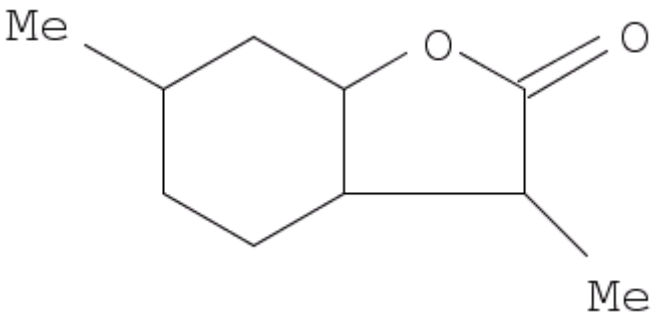
CAS NUMBER
92015-65-1

CHEMICAL NAME
2(3*H*)-Benzofuranone, hexahydro-3,6-dimethyl-

OTHER NAME(S)
Cyclohexaneacetic acid, 2-hydroxy-α,4-dimethyl-, γ-lactone (6CI,7CI)
Perhydro-3,6-dimethyl-benzo[b]furan-2-one
Koumalactone

MOLECULAR FORMULA
$C_{10}H_{16}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
168.23 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 95%

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: Colourless liquid (liquid may crystallise)

Property	Value	Data Source/Justification
Melting Point/Freezing Point	16 ± 0.5 °C	Measured
Boiling Point	275 °C at 99.7 kPa (decomposition temperature)	Measured
Density	1020 kg/m^3 at 20°C	Measured
Vapour Pressure	1.86 x 10^{-3} kPa at 25 °C	Measured
Water Solubility	2.7 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ = 4 days at pH 8.5, stable at pH 5 and 7	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.03 at 21 °C	Measured
Adsorption/Desorption	log K_{oc} = 1.98	Calculated (KOCWIN v2.00; US EPA, 2011)
Dissociation Constant	Not determined	Does not contain dissociable functionalities
Particle Size	Not determined	-
Flash Point	134 ± 2 °C at 102 kPa	Measured
Flammability limits	Not determined	-
Autoignition Temperature	>250 °C	Measured
Explosive Properties	Not determined	Not expected to be explosive based on structure
Oxidising Properties	Not determined	Not expected to be oxidising based on structure

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as:

- neat chemical for reformulation,
- a component in fragrance for reformulation into end-use products and
- a component of end-use products.

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

IDENTITY OF MANUFACTURER/RECIPIENTS
Notifier

TRANSPORTATION AND PACKAGING

The notified chemical or products containing the notified chemical will be imported in tightly closed lacquered drums of varying sizes: 180 kg, 100 kg, 50 kg, 25 kg, 10 kg or 5 kg. The notified chemical will be transported by road via commercial carrier truck for warehousing where it will be unloaded and stored in its original packaging for future distribution to customers, or will be directly transported to customers from the port of entry.

Reformulators will transport reformulated products in a variety of small package sizes (typical of consumer-sized containers) to retail stores by road.

USE
The notified chemical will be used as a fragrance ingredient in consumer products ranging from cosmetics (including personal care and fine fragrance) to household products (including air fresheners, all-purpose cleaners, cleaning products and laundry products). The content in the final consumer products will vary, with the proposed usage concentrations of ≤ 1% for air fresheners and ≤ 0.5% for cosmetic products and other household products.

OPERATION DESCRIPTION

Reformulation
When reformulated in Australia, the notified chemical or a mixture containing it will be blended into fragrance formulations or end-use consumer products at customer sites. A typical blending operation will be highly automated and conducted in a fully enclosed/contained environment. Local exhaust ventilation will also be employed. The transfer of ingredients into blending vessels and the transfer of the final formulation into containers will be conducted via automated, sealed delivery systems. Workers will also be involved in maintenance work on reformulation equipment. Empty drums used to transport the pure notified chemical or fragrance formulations will also be rinsed and re-used by workers.

Procedures for the formulation of final end-use products will vary depending on the nature of the cosmetic and household products being formulated. Both automated and manual steps may be involved. Workers will also oversee the steps, connect pump lines, sample periodically for quality control purposes, and fill containers with products.

End-use
Finished products containing the notified chemical (up to 1% concentration) may also be used by consumers and professionals such hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, the application could be varied – by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	Unknown	Unknown
Mixing	4	2
Drum handling	4	2
Drum cleaning	4	2
Maintenance	4	2
Quality control	0.5	1
Packaging	4	2
End-user	unspecified	unspecified

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come in contact with the notified chemical either in neat form or at various concentrations (in intermediate fragrance formulations and finished products) up to 5%, only in the event of accidental rupture of containers.

Reformulation

During reformulation of fragrance formulations, dermal, ocular and inhalation exposure of workers (up to 100% concentrations) may occur when handling the notified chemical or products containing it. Exposure is expected to be minimised through the use of local exhaust ventilation and/or automated/enclosed systems as well as through the use of PPE The notifier stated that workers will be required to wear the following personal protective equipment: gloves, respirator (if needed), eye protection, and protective clothing.

Exposure to the notified chemical in end-use products (up to 1% concentration) may also occur in professions that involve the use of cosmetic and household products (beauty salon and laundry workers and cleaners).

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of cosmetic and household products (at ≤ 0.5% concentration) and air fresheners (at ≤ 1% concentration). The principal route of exposure would be dermal, while ocular and inhalation exposures are also possible, particularly if products are applied by spray.

A combined internal dose of 1.46 mg/kg bw/day was estimated using data on typical use patterns on cosmetic and household cleaning product categories in which the notified chemical may be used (SCCS, 2010; Cadby *et al*, 2002; SDA, 2005; specific use details of the notified chemical are considered exempt information). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic and household products that may contain the notified chemical.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics, metabolism and distribution.

The notified chemical is of low molecular weight (168 Da) and has a log Pow of 2.03, suggesting a high potential for dermal absorption.

Acute toxicity.
The notified chemical is considered to be of low acute toxicity (LD50 > 2000 mg/kg bw) via the oral route based on a test conducted in rats. However the notified chemical may be of some concern if swallowed due to the nature of adverse clinical signs observed in the study.

No acute inhalation or dermal toxicity data were provided for the notified chemical.

Irritation and sensitisation.
The notified chemical was slightly irritating to skin and eyes in studies carried out on rabbits.

The notified chemical was not a skin sensitiser in a guinea pig maximisation test. One out of nineteen animals showed a positive response at challenge (observed only at the 24 hour observation period). This was deemed to be an irritant response due to the transient nature of the response.

Repeated dose toxicity.
In a 28-day repeat dose oral toxicity study in the rat (dose levels of 15, 150 and 1000 mg/kg bw/day) the No Observed (Adverse) Effect Level (NOAEL) was established by the study authors as 1000 mg/kg bw/day. The significance of some of the observed liver effects (increased liver weight in males and increased liver weight and liver gamma glutamyl transpeptidase levels in females) at 1000 mg/kg bw/day is not clear. Animals treated with 150 or 15 mg/kg bw/day showed no treatment-related changes in the organ weights measured.

Mutagenicity/Genotoxicity.
The notified chemical was non-mutagenic in a bacterial reverse mutation assay.

Health hazard classification

Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation
Dermal and ocular exposure of workers to the notified chemical (at 100% concentration) will occur during reformulation processes. As the notifier has stated that the exposure of workers is expected to be minimised through the use of automated processes, ventilated environments and wearing of PPE, the risk to these workers from use of the notified chemical is not considered to be unreasonable.

Cleaners and beauty care professionals may come in contact with products containing the notified chemical at ≤ 1% concentration. These products will also be available to the public. The exposure and risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2.).

6.3.2. Public Health

Members of the public may be repeatedly exposed to the notified chemical during the use of cosmetic products (≤ 0.5% concentration), air fresheners (≤ 1% concentration) and other household products (≤ 0.5% concentration).

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from the use of multiple products of 1.46 mg/kg bw/day (see Section 6.1.2.). Conservatively considering the mid dose concentration level (150 mg/kg bw/day) in the repeated dose toxicity study, the MoE was estimated to be 103. In general, a MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences.

Overall, based on the available information, the risk to the public from use of the notified chemical at ≤ 1% in air fresheners and ≤ 0.5% in cosmetic products and other household products is not considered to be unreasonable.

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 into Australia at 100% concentration or as a fragrance component of compounded formulations and various formulated end-use cosmetic and household products. Environmental release of the notified chemical during transportation and storage is expected to be minimal and will be limited to accidental spills or leaks of drums.

It is expected that the reformulation processes will involve blending operations that will be highly automated. It is expected to occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes. A total of 0.2% of waste is expected to be generated each from blending or formulation activities as a result of spills and residues.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to enter the aquatic compartment during use of the various end-use products into which it will be incorporated. Cosmetic products will be washed off the hair and skin and will be released to sewers. Cleaning products will also be diluted in water and will be released to sewers. It is estimated that a maximum of 3% of the consumer products will remain in the consumer containers once the consumer product is used up. These containers are expected to be sent to landfill or to be recycled.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that all spilled notified chemicals and clean up absorbent will be collected and placed in sealed containers for disposal to landfill. Containers containing residual notified chemical are expected to be released to landfill or to be recycled.

7.1.2. Environmental Fate

The notified chemical is not readily biodegradable based on the provided study report. For the details of the environmental fate study please refer to Appendix C. The notified chemical has a low log K_{OW} of 2.03, therefore, the bioaccumulative potential in aquatic organisms is not considered to be a concern.

The vapour pressure of the notified chemical of 1.86 Pa at 25°C provided by the notifier indicates a volatile potential. Based on a calculated (AOPWIN v 1.92; US EPA, 2011) half-life of 9.7 hours through atmosphere oxidation, it is not considered to be persistent in the air.

Most of the notified chemical is expected to be released into sewer systems after use of the associated products. A small amount of the notified chemical may be released to landfill as container residues or spills or thermally decomposed during containers' recycling, forming water and oxides of carbon. In landfill, the notified chemical may leach given the lowly expected adsorption/desorption constant (log K_{OC} = 1.98). In sewage treatment plants (STPs), the notified chemical removed by adsorption to sludge sediment is not expected to be a significant amount given the low log K_{OC}. The majority of the notified chemical is expected to be released into public waters. In water or soil/landfill, the notified chemical is expected to undergo biotic or abiotic degradation processes, forming water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the Predicted Environmental Concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleansing products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that none of the notified chemical will be removed during sewage treatment processes.

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)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

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 0.6 µg/L may potentially result in a soil concentration of approximately 4.039 µg/kg from each year of irrigation. 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 20.2 µg /kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data for the notified chemical were submitted. The ecotoxicity effects of the notified chemical were predicted using Ecological Structure Activity relationship (ECOSAR v1.11, US EPA 2012). The conservative toxicity results are summarised in the table below.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h EC50 = 26.4 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 54.9 mg/L	Harmful to *Daphnia*
Algal Toxicity	96 h EC50 = 23.7 mg/L	Harmful to alga

The notified chemical is considered to be harmful to aquatic organisms based on the above predicted endpoints. These data are for risk assessment purposes only. Modelled data are not used for the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009). Therefore, the notified chemical has not been formally classified under GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) was calculated using the predicted endpoint for alga which is considered to be the most sensitive species. An assessment factor of 1000 was used as measured ecotoxicological endpoints were not available for the notified chemical.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga)	23.7	mg/L
Assessment Factor	1000	
PNEC	23.7	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	23.7	0.026
Q - Ocean	0.06	23.7	0.003

The risk quotient (Q = PEC/PNEC) was calculated to be <<1 for discharge of effluent containing the notified chemical to the aquatic environment, indicating that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual use quantity.

Based on the calculated risk quotient and the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 16 ± 0.5 °C

Method EEC Commission Directive 92/69/EEC
Remarks The test was conducted according to good laboratory practice (GLP) principles.
Test Facility Safepharm (1995b)

Boiling Point 275 °C at 99.7 kPa (Decomposition temperature)

Method EEC Commission Directive 92/69/EEC, Method A2
Remarks The determination was carried out using the Siwoloboff Method. The test was conducted according to good laboratory practice (GLP) principles. As the test substance decomposed at atmospheric pressure, an attempt was also made to measure the boiling temperature at reduced pressure, however the substance failed to distil.
Test Facility Safepharm (1995b)

Density 1020 kg/m^3 at 20 ± 0.5 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Oscillating densitometer method. Value derived from relative density. Only a report summary was provided.
Test Facility Firmenich (2014)

Vapour Pressure 1.86 x 10^{-3} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
Remarks Dynamic method was used. Vapour pressure was measured by extrapolation after determining the boiling temperature at various specified pressures.
Test Facility Firmenich (1995)

Water Solubility 2.7 g/L at 20 °C

Method EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks Flask Method. The mixtures of the notified chemical with distilled water were shaken at approximately 30 °C for 24-72 hours, followed by standing at 20 °C for a period of not less than 24 hours. The mixtures were then centrifuged and analysed by gas chromatography. The mean concentration was determined to be 2.7 g/L at 20 °C. This was supposed to be the water solubility.
Test Facility Safepharm (1995b)

Hydrolysis as a Function of pH $t_{½}$ = 4 days at pH 8.5, stable at pH 5 and 7

Method OECD TG 111 Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ (days)*
5	40	Stable
7	40	Stable
8.5	40	4

Remarks The stability of the notified chemical was determined in a series of standard aqueous buffers at pH 2, pH 5, pH 7, pH 8.5 and pH 12 containing 1% of non ionic surfactant. The tests were done in accelerated conditions at 40°C for about one month. Gas chromatography with FID detector was used for the test concentration analysis.

After 5 days, the notified chemical showed disappearance of less than 10% at pH 2, 5 and 7 at 40°C. After 28 days, less than 10% of the notified chemical disappeared at pH 2 and 5 and 25% at pH 7 at 40°C. The half-life of the notified chemical at pH 8.5 and 12 at 40°C was determined to be 4 days and 0.25 days, respectively. The notified chemical is considered to

be not stable under basic conditions.

Test Facility Firmenich (2014b)

Partition Coefficient (n-octanol/water) log Pow = 2.03 at 21 °C

Method EC Council Regulation No 440/2008 A.8 Partition Coefficient
Remarks Flask Method. The partition coefficient was determined from the ratio of the solubilities of the notified chemical in n-octanol and water to be 108 (or log P_{OW} = 2.03) at 21 ± 0.5 °C
Test Facility Safepharm (1995b)

Flash Point 134 ± 2 °C at 102 kPa

Method EEC Commission Directive 92/69/EEC- Method A9
Remarks Closed cup method. The test was conducted according to good laboratory practice (GLP) principles.
Test Facility Safepharm (1995a)

Autoignition Temperature >250 °C

Method Internal method
Remarks Only a report summary was provided. No autoignition was reported at 250 °C (at 98.7 kPa) using 250 µL of the test substance and the "FIRELAB" instrument.
Test Facility Firmenich (2006)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity - Fixed Dose Method (adopted 17 July 1992).
Species/Strain	Rat/Sprague-Dawley
Vehicle	Maize oil
Remarks - Method	No significant protocol deviations.

RESULTS

Sighting Study

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

Signs of Toxicity	Piloerection and hunched appearance was noted in the animal dosed at 500 mg/kg bw (1/2 hour to 3 days after dosing). The animal treated at 2000 mg/kg bw showed piloerection, ataxia, subdued behaviour, hunched appearance, pale appearance and soiled coat (1/2 hour to 2 days after dosing).
Effects in Organs	None.

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
2000	5F/5M	2000	1F/0M

Discriminating Dose	2000 mg/kg bw
Signs of Toxicity	One female was killed *in extremis* 4 hours after dosing due to severity of reaction to treatment where prostration, tremors, laboured breathing, hunched appearance and piloerection were noted. The remaining animals displayed the following: piloerection, ataxia, subdued behaviour, hunched appearance, increased activity, encrusted eyes and red nasal discharge (1/2 hour to 7 days after dosing). Bodyweight gains were considered to be satisfactory.
Effects in Organs	Yellow/green fluid in the small intestine was noted in the female killed *in extremis*.
Remarks - Results	Since only one female died at 2000 mg/kg bw it was considered unnecessary to dose an additional group at 500 mg/kg bw because the study authors felt that it would provide limited new information and would not change the classification of the test. The body weight performance was considered to have been satisfactory. The study authors noted that the test substance, though likely to have an LD50 above 2000 mg/kg bw, may be of some concern if swallowed.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	IRI (1995)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	Similar to EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin

Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3F
Vehicle	None
Observation Period	7 days (for 2 of the 3 rabbits)
Type of Dressing	Semi-occlusive.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	1	1	< 7 days	0
Oedema	0	0	0	0	N/A	0

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

Remarks - Results	The reaction to treatment observed in one out of three animals was confined to barely perceptible erythema, apparent from 24 hours after the end of the contact period, which persisted up to the 72 hour observation period but was no longer observed 7 days after dosing.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY Toxicol Laboratories (1994a)

B.3. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD Similar to EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3F
Observation Period	72 hours

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0	0.33	1	< 48 hrs	0
Conjunctiva: chemosis	0	0	0	0	N/A	0
Corneal opacity	0	0	0	0	N/A	0
Iridial inflammation	0	0	0	0	N/A	0

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

Remarks - Results	All animals exhibited conjunctival redness (score of 1) one hour after dosing and in one animal was still evident at 24 hours.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Toxicol Laboratories (1994b)

B.4. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test.

Species/Strain	Guinea pig/Dunkin-Hartley (albino)
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 1% in maize oil (slight irritation) topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 20F Control Group: 10F
INDUCTION PHASE	Induction Concentration: intradermal: 10% in maize oil topical: 100%
Signs of Irritation	During the dose ranging test for induction, slight to severe reactions were noted at sights injected with the notified chemical at 25, 50, 75 and 100%. Slight reactions were noted at sights injected with 1, 2, 5, and 10%. No irritation was noted at topically treated sites. In the main test slight to moderate irritation was noted in the test group while slight irritation was noted in the control group.
CHALLENGE PHASE	
1st challenge	topical: 100%
Remarks - Method	Four guinea pigs were used in a dose ranging test for challenge. These animals were pre-treated during the induction phase with Freund's Complete Adjuvant only and the test material (at 25, 50, 75 and 100%). Positive controls were routinely conducted (six-monthly intervals) in the facility using 2-mercaptobenzothiazole (MBT) at induction concentrations of 5% (injection) and 75% (topical) and at challenge concentrations of 10 and 75% w/v in maize oil. In the most recent positive control using 75% and 10% MBT at challenge, 89% and 78% respectively of the test group reacted positively.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge:*	
		24 h	*48 h*
Test Group	100%	1/19	0/19
Control Group	100%	0/9	0/9

Remarks - Results	One test group animal was killed *in extremis* approximately 24 hours after patch application during topical induction because it was convulsing, shaking and vocalising. No clinical signs except reactions induced by treatment were noted in the remaining test and control animals. During the dose ranging test for challenge no irritation was noted at sites treated with the test material (at 25, 50, 75 and 100%). One of the ten control group animals died during the challenge phase (cause of death unknown). Though none of the control animals which had previously only been exposed to the vehicle maize oil showed a positive reaction to challenge with the test substance, one of these control animals reacted positively to challenge with maize oil. The positive response noted in one of the test group animals at challenge (observed at 24 hour observation period) was deemed by the study authors to be an irritant response due to its transient nature (not observed at the 48 hour observation period).
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	IRI (1994)

B.5. 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/Sprague-Dawley Crl:CD BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Arachis oil BP

RESULTS

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

No treatment related effects on food and water consumption were noted at any dose level.

No treatment related effects on body weights was noted at any dose level. Statistically significant slight increase in mean body weight gain was noted in females at the high dose during week 1 of treatment only.

Mortality and Time to Death
There were no unscheduled deaths.

Clinical Observations
The following clinical signs, often accompanying the oral administration of test substance formulation and are considered to be attributable to an unpleasant tasting of locally irritant formulation, were observed though not considered indications of systemic toxicity:

Treatment	Females	Males
1000	increased salivation, red/brown staining around the fur, mouth and snout	increased salivation, red/brown staining around the mouth
150	increased salivation	increased salivation

The observed fur loss in high dose animals (and wet fur in males) was considered by the study authors as common in rats of the strain and age used in the study.

Functional Observations
There were no treatment related changes in behaviour, functional performance and sensory reactivity.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There were no treatment related changes in the measured haematological parameters.

The following blood chemistry changes (statistically significant) were noted:

Treatment	Females	Males
1000	↓chloride	↓phosphorus, ↓alkaline phosphatase
15	↓chloride	

The changes seen in blood inorganic phosphorus were not considered of toxicological importance by the study authors because individual values were not outside the normally expected range for rats of the strain and age used and there were no accompanying effects noted in blood calcium.

There was no dose response relationship in the changes in chloride levels seen in females as effects were not noted in mid dose females.

Effects in Organs
The following statistically significant changes were noted:

Treatment	Females	Males
1000	↑liver weight (relative to terminal body weight), ↑liver weight (absolute), ↑liver gamma glutamyl transpeptidase	↑liver weight (relative to terminal body weight)

Many of the individual relative values for organ weight changes were outside the normally expected respective ranges for rats of the strain and age used.

At necropsy, one male treated at high dose and one male treated at mid dose showed patchy pallor and mottled appearance of kidneys; this effect was not seen in the low dose and control groups and no female animals exhibited this effect at any dose level.

The following were significant histopathological changes noted:

Treatment	Females	Males
1000	centrilobular hepatocyte enlargement	centrilobular hepatocyte enlargement; ↑incidence/severity of globular eosinophilic accumulations in renal proximal tubules
150	centrilobular hepatocyte enlargement	centrilobular hepatocyte enlargement
15		centrilobular hepatocyte enlargement

The histopathological changes in kidney tubule epithelia are peculiar to adult male rats and therefore of no human relevance. The study authors considered the hepatocyte enlargement to be adaptive to the administration of xenobiotics, in the absence of associated inflammatory or degenerative changes.

Remarks – Results
The study authors established a No Observed (Adverse) Effect Level (NO(A)EL) of 1000 mg/kg bw/day for the notified chemical. However the statistically significant changes in organ effects seen in both male (increased liver weight) and female (increased liver weight and liver gamma glutamyl transpeptidase levels) animals at 1000 mg/kg bw/day, outside the normally expected respective ranges for rats of this strain and age, cannot be discounted even though the significance of these effects are not clear.

CONCLUSION
The effects noted for male and female animals in the high dose group were considered by the study authors to be non-adverse. Therefore, the No Observed (Adverse) Effect Level (NO(A)EL) was established by the study authors as 1000 mg/kg bw/day.

TEST FACILITY Safepharm (1998)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure
Species/Strain *S. typhimurium*: TA1538, TA1535, TA1537, TA98 and TA100
Metabolic Activation System S9 fraction from Aroclor induced rat liver
Concentration Range in a) With metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate

Main Test	b) Without metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	A preliminary test using TA100 bacterial suspension (0 – 5000 µg/plate) was conducted to determine the toxicity of the test substance.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Preliminary test	≥ 5000		-	
Test 1		≥ 5000	-	Negative
Test 2		≥ 5000	-	Negative
Present				
Test 1		> 5000	-	Negative
Test 2		> 5000	-	Negative

Remarks - Results	The preliminary study showed that the test substance was non-cytotoxic to the TA100 strain however a reduction in revertants was evident at the highest dose. In the main tests, a slight decrease in the frequency of revertant colonies was observed with several strains tested at higher dose levels; however there was no visible reduction in the growth of the bacterial background lawn. The positive controls showed the expected increase in revertant colonies.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm (1994)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	A mixed population of sewage treatment micro-organisms
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The biochemical oxygen demand (BOD) was determined for determination of the degradation degree
Remarks - Method	The study followed the above test guideline and good laboratory practice (GLP) principles. The test was conducted at a concentration of 1.5 mg/L. Control solutions with inoculum and the reference item sodium benzoate (3mg/L), together with a toxicity control (1.5 mg notified chemical/L and 1.5 mg sodium benzoate/L) were used for validation purposes.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	14	6	99
28	26	28	96

Remarks - Results	All the test validity criteria were met. The toxicity control reached 31% degradation by 28 day, indicating the notified chemical is not toxic to the micro-organisms. The test results in the table above indicate that the notified chemical is not readily biodegradable. The test results in the table above indicate that the notified chemical is not readily biodegradable.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Safepharm (1995c)

BIBLIOGRAPHY

Cadby, PA, Troy, WR and Vey, MGH (2002) Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation. Regulatory Toxicology and Pharmacology, 36: 246-252.

enHealth (2004) Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Canberra, Department of Health and Ageing and enHealth Council, Commonwealth of Australia.

EC (2003). Technical Guidance Document on Risk Assessment in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances and Directive 98/8/EC of the European Parliament and of the Council Concerning the Placing of Biocidal Products on the Market – Part II. Institute for Health and Consumer protection, European Chemicals Bureau, European Communities. Available at <http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/doc/tgd>.

Firmenich (2014b) Stability Test of Perfumery Raw Materials (Document date: May, 2014). Geneva, Switzerland, Firmenich S.A Geneva (Unpublished report submitted by the notifier).

IRI (1994) [Notified chemical] Magnusson-Kligman maximisation test in guinea pigs (Project No. 555132, May 1994). Tranent, Scotland, Inveresk Research International Limited (Unpublished report submitted by the notifier).

IRI (1995) [Notified chemical] Acute oral toxicity test in rats – fixed dose procedure (Project No. 555567, June 1995). Tranent, Scotland, Inveresk Research International Limited (Unpublished report submitted by the notifier).

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

NTC (National Transport Commission) 2007 Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), 7th Edition, Commonwealth of Australia.

Safepharm (1995a) [Notified chemical] Determination of flash point (Project No. 161/014, March, 1995). Derby, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

Safepharm (1995b) [Notified chemical] Determination of general physico-chemical properties (Project No. 161/013, April, 1995). Derby, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

Firmenich (1995) [Notified chemical] Vapour pressure test summary (Report No. 1969(E)-FPR, 2 August 1995). Geneva, Switzerland, Process Safety and Analytical Development Laboratory (Unpublished report submitted by the notifier).

Firmenich (2006) [Notified chemical] Autoignition temperature test summary (Report No. 8435-FPR, 14 February 2006). Geneva, Switzerland, Franco Ferregutti Safety Laboratory (Unpublished report submitted by the notifier).

Firmenich (2014a) [Notified chemical] Relative density test summary (Document date: 10 June 2014). Geneva, Switzerland, Process Safety and Analytical Development Laboratory (Unpublished report submitted by the notifier).

Safepharm (1994) [Notified chemical] Reverse mutation assay "Ames Test" using *Salmonella typhimurium* (Project No. 161/15, November, 1994). Derby, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

Safepharm (1995c) Assessment of the ready biodegradability (Closed Bottle Test) of [Notified chemical] Project No. 161/32, January, 1995). Derby, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

Safepharm (1998) [Notified chemical] Twenty-eight day repeated dose oral (gavage) toxicity study in the rat (Project No. 161/161, June, 1998). Derby, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

SDA (2005) Exposure and Risk Screening Methods for Consumer Product Ingredients. Washington DC USA, The Soap and Detergent Association.

SCCS (2012) Notes of Guidance for testing of Cosmetic Ingredients and Their Safety Evaluation (8th revision). European Commission - Scientific Committee on Consumer Safety.

SWA (2012) Code of Practice: Managing Risks of Hazardous Chemicals in the Workplace, Safe Work Australia, http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/managing-risks-of-hazardous-chemicals-in-the-workplace.

Toxicol Laboratories (1994a) Acute dermal irritation study in the rabbit [Notified chemical] (Study No A/S/40761, October, 1994). Herefordshire, UK, Toxicol Laboratories Ltd (Unpublished report submitted by the notifier).

Toxicol Laboratories (1994b) Acute eye irritation study in the rabbit [Notified chemical] (Study No A/S/40762, October, 1994). Herefordshire, UK, Toxicol Laboratories Ltd (Unpublished report submitted by the notifier).

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS), 3rd revised edition. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >.

US EPA (2011) Estimation Programs Interface (EPI) Suite™ for Microsoft® Windows, v 4.10. United States Environmental Protection Agency. Washington DC, USA.