File No: LTD/1746

June 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Vanincol

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:

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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/1746	Firmenich Pty Ltd	Vanincol	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 safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation processes:
  - Avoid contact with eyes

  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.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should 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

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 notified chemical is proposed to be used at > 12% for air fresheners and > 0.3% for other household products, > 2.2% for fine fragrances, > 2% for shower gels and > 0.5% for other cosmetic products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a 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.

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

ASSESSMENT DETAILS

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 and structural formulae, molecular weight, degree of purity, impurities and additives/adjuvants

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: adsorption/desorption and dissociation constant

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Vanincol

MOLECULAR WEIGHT
< 500 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: extremely pale yellow crystalline solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	52.3 °C at 98.7 kPa	Measured
Boiling Point	275 °C at 97.6 kPa	Measured
Density	1161 kg/m^3 at 20 °C 1290 kg/m^3 at 25 °C	Measured
Vapour Pressure	1×10^{-4} kPa at 25 °C	Measured
Water Solubility	0.376 g/L at ± 20 °C	Measured
Hydrolysis as a Function of pH	After 28 days (40 °C) ~ 5% Degradation (pH < 5) ~ 28% Degradation (pH 7) 100% Degradation (pH ≥ 8.5)	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.27 at 30 °C	Measured

Adsorption/Desorption	log K_{oc} = 1.9	Calculated (using KOCWIN v2.00; US EPA, 2009)
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Inhalable fraction (< 100 μm): 6%	Measured
Flash Point	153 °C at 101.3 kPa	Measured
Flammability	Not highly flammable	Measured
Autoignition Temperature	Not below the melting temperature	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidising properties.

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 not be manufactured in Australia. The notified chemical will be imported into Australia as a component (≤ 30%) 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
Firmenich Limited

TRANSPORTATION AND PACKAGING
The notified chemical (≤ 30% concentration) will be imported into Australia in lacquered drums of typically 180 kg size, but the use of smaller containers down to 5 kg is also possible. The products containing the notified chemical will be transported from the port of entry by road to the notifier's warehouse facilities for storage and then distributed to reformulation sites. The end-use products (≤ 12% notified chemical) will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products. Household products containing the notified chemical are expected to include air fresheners, all-purpose cleaners, detergents, fabric softeners, hard surface wipes, furniture/window cleaner, dish wash and lavatory care. The content in the final consumer products will vary, with the proposed usage concentrations of ≤ 12% for air fresheners and ≤ 0.3% for other household products, ≤ 2.2% for fine fragrances, ≤ 2% for shower gels and ≤ 0.5% for other cosmetic products including hair spray.

OPERATION DESCRIPTION
The procedures for incorporating the imported fragrance preparations (containing ≤ 30% notified chemical) into end-use products will likely vary depending on the nature of the cosmetic and personal care/household products

being formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in enclosed environments, followed by automated filling of the reformulated products into containers of various sizes.

The finished products containing the notified chemical at ≤ 12% concentration may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, these could be applied in 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

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	unknown	unknown
Mixer	4	2
Drum Handling	4	2
Drum Cleaning	4	2
Quality Control	0.5	1
Packaging	4	2

EXPOSURE DETAILS

Transport and storage workers may come into contact with the notified chemical, as a component of the imported fragrance preparations (≤ 30% concentration) or end-use products (≤ 12% concentration), only in the event of accidental rupture of containers.

During reformulation of the notified chemical into the final consumer products, dermal, ocular and inhalation exposure of workers (at ≤ 30% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of local and general ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as coveralls, safety glasses, face masks and impervious gloves.

Exposure to the notified chemical in end-use products (at ≤ 12% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons) or in the cleaning industry. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at various concentrations, such as ≤ 12% for air fresheners and ≤ 0.3% for other household products, ≤ 2.2% for fine fragrances, ≤ 2% for shower gels and ≤ 0.5% for other cosmetic products) through the use of the household products and the rinse-off and leave-on cosmetic and personal care products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2010; Cadby *et al.*, 2002; SDA, 2005). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes (European Commission, 2003). For the inhalation exposure assessment (European Commission, 2003; SDA, 2005), an adult inhalation rate of 23 m^3/day (enHealth, 2004) was used and it was assumed that the bioavailability of the notified chemical via the inhalation route is 100%. An adult bodyweight of 60 kg was used for calculation purposes.

- Cosmetic products (Dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.5	1	0.65
Face cream	1540	0.5	1	0.13
Hand cream	2160	0.5	1	0.18
Fine fragrances	750	2.2	1	0.28
Deodorant spray	1430	0.5	1	0.12
Shampoo	10460	0.5	0.01	0.01
Conditioner	3920	0.5	0.01	0.00
Shower gel	18670	2	0.01	0.06
Hand soap	20000	0.5	0.01	0.02
Hair styling products	4000	0.5	0.1	0.03
Total				1.48

C = concentration (%); RF = retention factor.
Daily systemic exposure = (Amount × C × RF × dermal absorption)/body weight

- Household products (Indirect dermal exposure - from wearing clothes):

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.3	0.95	10	0.012
Fabric softener	90	0.3	0.95	10	0.003
Total					0.015

Daily systemic exposure = (Amount × C × PR × PT × dermal absorption)/body weight

- Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.3	1980	0.01	0.01	0.007	0.00009
Dishwashing liquid	3	0.3	1980	0.0093	0.01	0.03	0.00081
All-purpose cleaner	1	0.3	1980	1	0.01	0.007	0.0069
Total							0.0078

Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor x dermal absorption)/body weight

- Household products (Inhalation exposure):

Product type	Frequency (use/day)	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration (mins)	Airspace volume (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	2	10	0.3	23	15	2	0.12

Daily systemic exposure = (Frequency × Amount × C × Inhalation rate × Exposure duration × bioavailability via the inhalation route)/(body weight × Airspace volume)

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 1.623 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, in particular assuming an airspace volume of 2 m^3, and the aggregate exposure from use of the dermally applied products, which

assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners).

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
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 3.52 mg/L/4 hours; inconclusive
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose toxicity - 28 days	NOAEL = 650 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration	non genotoxic

Toxicokinetics

Based on the water solubility (0.376 g/L at 20 ºC), partition coefficient (log P_{ow} = 2.27) and the low molecular weight (< 500 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption could occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity

In studies conducted in rats the notified chemical was found to have low acute oral and dermal toxicity.

An acute inhalation toxicity study (nose only) was conducted in rats (3 per sex) with the notified chemical at a mean maximum attainable dust atmosphere concentration of 3.52 mg/L for 4 hours. There were no mortalities during the study. Test substance related changes observed were increased respiratory rate and slight bodyweight losses. All animals appeared normal 5 days post-exposure. The LC50 was therefore determined to be greater than 3.52 mg/L. Given a test atmosphere concentration of greater than 5 mg/L could not be achieved, the study is inconclusive for determining the hazard classification of the notified chemical.

Irritation

Based on studies conducted in rabbits the notified chemical was non-irritating to the skin and slightly irritating to eyes.

Sensitisation

The notified chemical at concentrations up to 50% in a mouse Local Lymph Node Assay showed no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation.

Repeated dose toxicity

A 28 day repeat dose study by oral gavage was conducted in rats with the notified chemical at dose levels of 30, 300 and 650 mg/kg bw/day. The changes identified as centrilobular hepatocellular hypertrophy of the liver and increased incidence and severity of follicular hypertrophy of the thyroid for males treated with 650 mg/kg/day were considered adaptive in nature, hence the No Observed Adverse Effect Level (NOAEL) was established as 650 mg/kg bw/day.

Mutagenicity/Genotoxicity

The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

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

Hairdressers, beauticians, cleaners and sales workers may be exposed to the notified chemical at various concentrations when applying products containing it to clients. The risk for beauty care professionals who regularly use products containing the notified chemical is expected to be similar to that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment, see Section 6.3.2.

Workers involved in the reformulation of the imported products into cosmetic products may be exposed to the notified chemical at concentrations up to 30%. Exposure is expected to be limited during product reformulation by the engineering controls and the PPE used.

Under the proposed occupational settings the notified chemical is not considered to pose an unreasonable risk to workers.

6.3.2. Public Health

The general public will be repeatedly exposed to the notified chemical during the use of both rinse-off and leave-on cosmetics, toiletries and household products containing the notified chemical at various concentrations, such as ≤ 12% for air fresheners and ≤ 0.3% for other household products, ≤ 2.2% for fine fragrances, ≤ 2% for shower gels and ≤ 0.5% for other cosmetic products.

Local effects

The notified chemical is slightly irritating to the eyes. However at the low proposed end use concentrations eye irritation effects are not expected.

Systemic effects

The potential systemic exposure to the public from the use of the notified chemical in cosmetic and household products was estimated to be 1.623 mg/kg bw/day. Using a NOAEL of 650 mg/kg bw/day, which was derived from a 28 day repeated dose toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 400. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences, therefore, the MOE is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at the proposed usage concentration of ≤ 12% for air fresheners and ≤ 0.3% for other household products, ≤ 2.2% for fine fragrances, ≤ 2% for shower gels and ≤ 0.5% for other cosmetic 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 as a component of fragrance preparations for local reformulation into a variety of consumer products (cosmetics, household products, fine fragrances). Release during reformulation in Australia is expected to arise from spills (0.1%), formulation equipment cleaning (no release estimate as cleaning water is recycled) and residues in import containers (0.1%). Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill. Import containers will either be recycled or disposed of through an approved waste management facility. Therefore, up to 0.2% or up to 2 kg the import volume is estimated to be released to landfill as a result of reformulation in Australia.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to sewers in domestic situations across Australia as a result of its use in cosmetic and domestic products, which are either washed off the hair and skin of consumers, or disposed of following cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated that a maximum of 3% or up to 3 kg of the notified chemical will remain in end-use containers. These will be disposed of through domestic garbage disposal and will enter landfill or be recycled.

7.1.2. Environmental Fate

Following its use in Australia as a fragrance in cosmetics and domestic products, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. Based on its low adsorption coefficient (log Koc = 1.9) only limited partitioning to sludge is expected. The notified chemical is readily biodegradable (> 85%) and is expected to degrade during sewage treatment process. It is not likely to bioaccumulate based on its low partition coefficient (log Kow = 2.27). If released to surface waters, the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The half-life of the notified chemical in air is calculated to be 3 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA, 2009). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

A proportion of notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. Notified chemical residues in landfill, soil and sludge are expected to have high mobility based on its high water solubility and its predicted soil adsorption coefficient (log K_{oc} = 1.9). As the notified chemical is readily biodegradable, it is not expected to persist in the terrestrial compartment and is expected to degrade to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

Since most of the notified chemical will be washed into the sewer, under a worst case scenario, with no removal of the notified polymer in the sewage treatment plant, the resultant Predicted Environmental Concentration (PEC) in sewage effluent on a nationwide basis is estimated as follows:

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 0.606 µg/L may potentially result in a soil concentration of approximately 4.039 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 20.19 µg/kg and 40.39 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Acute		
Fish	96 h LC50 = 4.22 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 = 4.1 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 62 mg/L	Harmful to algae
Micro-organism	3h EC50 = 270 mg/L	Not expected to inhibit microbial respiration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is toxic to fish and aquatic invertebrates and is formally classified as 'Acute Category 2: Harmful to aquatic life. The notified chemical is readily biodegradable and based on its low partition coefficient (log Kow 2.27), it is not expected to bioaccumulate. Therefore, the notified chemical has not been formally classified for its long-term hazard under the Globally Harmonised System of Classification and Labelling of Chemicals.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the acute Daphnia toxicity of the notified chemical and an assessment factor of 100 as measured acute endpoints are available for three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Daphnia).	4.1	mg/L
Assessment Factor	100	
PNEC:	41	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:	0.61	41	0.015
Q - Ocean:	0.06	41	0.0015

The risk quotient for discharge of effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. The notified chemical has a low potential for bioaccumulation and is unlikely to persist in surface waters, soil or air. Therefore, on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 52.3 ± 0.5 °C at 98.7 kPa

Method OECD TG 102 Melting Point/Melting Range.
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks The capillary method: BS4634 method was used.
Test Facility Firmenich (2011)

Boiling Point 275 ± 2 °C at 97.6 kPa

Method OECD TG 103 Boiling Point.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks The Siwoloboff method was used.
Test Facility Firmenich (2011)

Density 1161 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 The Oscillating density meter method was used.
Test Facility Firmenich (2011)

Density 1290 kg/m^3 at 25.0 ± 0.5 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks A gas comparison pycnometer was used.
Test Facility Harlan Laboratories Ltd (2013a)

Vapour Pressure 1×10^{-4} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks The gas saturation method was used.
Test Facility Harlan Laboratories Ltd (2012a)

Water Solubility 0.376 g/L at 20 ± 0.5°C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method. Analysed by HPLC.
Test Facility Firmenich (2011a)

Hydrolysis as a Function of pH After 28 day, 40°C
~ 5% Degradation (pH < 5)
~ 28% Degradation (pH 7)
100% Degradation (pH ≥ 8.5)

Method In-house

pH	*T (°C)*	*% hydrolysis after 5 days**	*% hydrolysis after 28 days**
2	40	0	0
5	40	5	5
7	40	12	28
8.5	40	80	100
12	40	100	100

*Approximate values read from graph.

Remarks	Test substance (200 – 300 ppm) was dissolved in in buffer solutions (types A, C, D, F and I: Reference Handbook of Chemistry and Physics) containing 1% non-ionic surfactant (Arkopal N 150) and put into storage in an oven at 40 °C over 28 days. Aliquots of test solution were extracted with organic solvent (typically cyclohexane or ethyl acetate) containing a hydrocarbon standard (typically C12, C17 or C20) on a regular basis throughout the test and analysed by GC-FID. After 28 days at 40°C the rate of hydrolysis was ~ 5% at pH < 5, 28% at pH 7 and 100% at pH ≥ 8.5. The results indicate that the notified chemical has the potential to hydrolyse under environmental conditions.
Test Facility	Firmenich (2012)

Partition Coefficient (n-octanol/water) log Pow = 2.27 at 30 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method
Test Facility	Firmenich (2011a)

Particle Size The test substance was considered to be essentially non-inhalable by study authors.

Method European Commission Technical Guidance Document EUR 20268 'Determination of Particle Size Distribution, Fibre Length and Diameter Distributions of chemical substances' (2002).

Range (μm)	*Mass (%)*
< 100	6

Remarks	The proportion of test substance through a 100 μm sieve was determined using an Inclyno sieve shaker.
Test Facility	Harlan Laboratories Ltd (2013b)

Flash Point 153 ± 2 °C at 101.325 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	A closed cup equilibrium method was used.
Test Facility	Firmenich (2011)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks	The test substance failed to ignite in the preliminary screening test.
Test Facility	Harlan Laboratories Ltd (2012b)

Autoignition Temperature Not below the melting point of the test substance

Method	EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks	While heating the test substance to 64 ºC no relevant exothermic reaction self-heating of the sample was observed. On completion of the test, the test substance had melted.
Test Facility	Harlan Laboratories Ltd (2012b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure. EC Council Regulation No 440/2008 B.1 bis Acute toxicity (oral) fixed dose method.
Species/Strain	Rat/Wistar
Vehicle	Arachis oil BP
Remarks - Method	No protocol deviations.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	There were no unscheduled deaths during the study. No signs of systemic toxicity were noted during the observation period in the 300 mg/kg group. Clinical signs that were observed in the treated animals in the 2000 mg/kg groups included hunched posture, lethargy, ataxia, pilo-erection, ptosis, prostration and increased lacrimation. Animals appeared normal one or three days after dosing.
Effects in Organs	No adverse macroscopic findings were recorded at necroscopy.
Remarks - Results	All animals showed expected gains in bodyweight over the study period.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Harlan Laboratories Ltd (2012c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/Wistar
Vehicle	Moistened with arachis oil BP
Type of dressing	Semi-occlusive.
Remarks - Method	No protocol deviations.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema was noted at the test sites of all animals. Test sites appeared normal two or three days after dosing,
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted during the observation period
Effects in Organs	No adverse macroscopic findings were recorded at necroscopy.

Remarks - Results	All animals showed expected gains in bodyweight over the study period, except for two animals which showed no gain in bodyweight or bodyweight loss during the first week but had expected gain in bodyweight during the second week.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Harlan Laboratories Ltd (2012d)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 436 Acute Inhalation Toxicity – Acute Toxic Class Method.
Species/Strain	Rats/RccHan WIST
Vehicle	Water
Method of Exposure	Oro-nasal exposure.
Exposure Period	4 hours
Physical Form	Solid aerosol (particulate).
Particle Size	MMAD (mean mass median aerodynamic diameter) 5.56 μm GSD (geometric standard deviation) 3.07 Inhalable fraction (% < 4 μm) 38.4 (predicted)
Remarks - Method	The chamber concentration was measured at regular intervals. Four samples were found to be 20% outside of the mean achieved atmosphere concentration (two low and two high). The study authors state that the test substance was generated at the maximum speed that the generation system could run at in order to achieve the maximum attainable atmosphere concentration during the exposure and that the nominal concentration also showed that keeping the aerosol airborne was extremely difficult. These deviations were therefore considered to be unavoidable. The particle size distribution and GSD that were achieved during the study were outside the ranges specified in the test guidelines (i.e. 1- 4 μm and 1.5-3.0). The percentage of particles of < 4 μm was predicted to be 38.4%. The study authors claim that the test atmosphere could not be improved without lowering the mean achieved atmosphere concentration as it was limited by the physical nature of the test substance.

RESULTS

Number and Sex of Animals	*Concentration <mg/L>*		*Mortality*
	Nominal	*Actual*	
3 per sex	47.6	3.52 ± 0.54	0

LC50	> 3.52 mg/L/4 hours
Signs of Toxicity	Hunched posture, pilo-erection, red/brown staining around the eyes or snout and wet fur was noted in all animals during exposure, on removal from the chamber and one-hour post exposure. These observations are considered by the study author to be associated with the restraint as these are commonly observed during 4-hour inhalation studies. Increased respiratory rate was also observed in all animals. Animals recovered to appear normal from days 3 to 5 post-exposure.
Effects in Organs	Dark patches on the lungs were detected amongst two animals at necropsy.
Remarks - Results	Slight bodyweight loss was noted for all male animals and one female animal on the first day post-exposure. Reasonable bodyweight gain was noted for all animals for the remainder of the exposure period except for one female animal which exhibited a slight bodyweight loss from days 1 to 3 post-exposure.

CONCLUSION The notified chemical is harmful via inhalation.

TEST FACILITY Harlan Laboratories Ltd (2012e)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	Moistened with distilled water
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No protocol deviations.

RESULTS

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

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

Remarks - Results 3-minute, 1-hour and 4-hour applications of the test substance to the intact skin of rabbits produced no evidence of skin irritation.

All animals showed the expected gains in bodyweight over the study period.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Harlan Laboratories Ltd (2012f)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	72 hours
Remarks - Method	No protocol deviations.

A Rabbit Enucleated Eye Test (REET) performed prior to the *in vivo* test indicated that the test substance was unlikely to cause severe ocular irritancy.

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	0.3	0.3	1	< 72 hours	0
Conjunctiva: chemosis	0.3	0.3	0.3	1	< 48 hours	0
Conjunctiva: discharge	0	0	0	0	-	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

Moderate conjunctival irritation was noted in all treated eyes one hour after treatment with minimal conjunctival irritation noted at the 24-hour observation. Minimal conjunctival redness persisted in one treated eye at the 48-hour observation.

Two treated eyes appeared normal at the 48-hour observation and one treated eye appeared normal at the 72-hour observation.

All animals showed the expected gains in bodyweight over the study period.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Harlan Laboratories Ltd (2012g)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse/CBA/Ca

Vehicle: Acetone:olive oil (4:1)

Remarks - Method: No protocol deviations.

Topical application was made to the dorsal surface of the ear. A concurrent positive control study was not run, but previously conducted positive control data from the test laboratory was provided.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	2405.58	-
10	5704.63	2.37
25	5462.53	2.27
50	6571.70	2.73
Positive Control (α-hexycinnamaldehyde)		
25	not reported	4.05

Remarks - Results

No mortalities and no signs of systemic toxicity were noted in the test or control animals.

The results show that the test substance elicited stimulation indices < 3.

The positive controls gave satisfactory responses confirming the validity of the test system.

CONCLUSION

There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY

Harlan Laboratories Ltd (2012h)

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	Rats/Wistar Han:RccHan:WIST
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Arachis oil BP
Remarks - Method	No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	1
low dose	5 per sex	30	0
mid dose	5 per sex	300	0
high dose	5 per sex	650	0

Mortality and Time to Death

One control male died during the bleeding procedure on day 28 of the study. This death was considered procedure related therefore is of no toxicological significance. There were no further unscheduled deaths during the study.

Clinical Observations

Analysis of functional observations, behaviour assessments, functional performance, sensory reactivity, body weight and food and water consumption did not reveal any toxicologically significant abnormalities between the treated and the control groups. Clinical signs that some test animals exhibited above 300 mg/kg bw/day, such as increased salivation, were dismissed by the study authors as commonly observed following the oral administration of unpalatable test substance formulations and in isolation were not considered to be of toxicological importance.

Increased respiratory rate was recorded for one male treated with 650 mg/kg bw/day on day 19 only, whilst another male at this dose level showed ataxia and lethargy on day 23 and ataxia was also recorded for two males and one female on day 27. These were isolated incidents which were transient in its nature and were considered of limited toxicological relevance by study authors.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no toxicologically significant effects detected in the haematological parameters investigated.

For blood chemistry investigation, males treated with 650 mg/kg bw/day showed a statistically significant increase in total cholesterol and bile acids concentration.

No toxicologically significant effects were detected in females treated with 650 mg/kg bw/day or in animals of either sex treated with 300 or 30 mg/kg bw/day.

Effects in Organs

There were no macroscopic abnormalities detected in all treated animals at necropsy.

Males treated with 650 mg/kg bw/day showed statistically significant increase in liver and thyroid weights, both absolute and relative to terminal body weights.

No such effects were detected in the organ weights measurement in males treated with 300 or 30 mg/kg bw/day and in all treated females.

Treatment related changes in histopathological examinations included the following: centrilobular hepatocellular hypertrophy and increased hepatocellular glycogen contents in liver were recorded in males

treated with 650 mg/kg bw/day; increased incidence and severity of follicular hypertrophy in thyroid gland was detected in males treated with 650 mg/kg bw/day.

The remaining microscopic findings recorded in this study were within the range of normal background lesions which may be recorded in animals of this strain and age.

Remarks – Results

For males treated with 650 mg/kg bw/day, histopathological examination of the liver revealed centrilobular hepatocellular hypertrophy and increased hepatocellular glycogen contents. This finding was supported with organ weight data such as increased absolute and relative liver weights. However, in the absence of any degenerative or inflammatory changes, this was considered by study authors to be adaptive in nature. Microscopic examination of the thyroid revealed increased incidence and severity of follicular hypertrophy in males treated at the same dose level and it correlated to increased absolute and relative thyroid weights in these animals. The thyroid and liver changes are characteristic of a consequence of hepatocellular induction as a result of enhanced hepatic metabolism. As a side effect of hepatic induction an increased liver metabolism of thyroid hormones T3 and T4 can occur. This subsequently leads to an enhanced thyroid gland production of these hormones as a consequence of a negative feedback stimulation of TSH production. The appearance of thyroid follicular hypertrophy is considered to be a result of this process. Study authors concluded that blood chemical findings of increased total cholesterol and bile acids concentration in males treated at the same dose level were probably associated with these metabolic changes.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 650 mg/kg bw/day in this study, based on the fact that the changes identified as centrilobular hepatocellular hypertrophy of the liver and increased incidence and severity of follicular hypertrophy of the thyroid are considered by study authors to be adaptive in nature.

TEST FACILITY Harlan Laboratories Ltd (2012i)

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/Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	Test 1 (range-finding test) used the direct plate incorporation method while test 2 (main test) used pre incubation method.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 5,000	> 5,000	negative
Test 2	> 5,000	> 5,000	negative
Present			
Test 1	> 5,000	> 5,000	negative
Test 2	> 5,000	> 5,000	negative

Remarks - Results No test substance precipitate was observed at any of the doses tested in either the presence or absence of S9-mix.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

The positive controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

The test substance caused no visible reduction in the growth of the bacterial background lawn at any dose level and was therefore tested up to the maximum recommended dose level of 5000 µg/plate.

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

TEST FACILITY Harlan Laboratories Ltd (2012j)

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 phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	Vehicle and positive controls (mitomycin C without metabolic activation and cyclophosphamide with metabolic activation) were used in parallel with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 250, 500, 750*, 1000*, 1250*, 1500*	4 h	24 h
Test 2	0*, 15.63, 31.25*, 62.5*, 125, 250*, 375, 500	24 h	24 h
Present			
Test 1	0*, 250, 500*, 750, 1000*, 1250*, 1500*	4 h	24 h
Test 2	0*, 500, 750, 1000*, 1125, 1250*, 1375*, 1500, 1625	4 h	20 h

*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	≥ 1962	≥ 1500	≥ 1250	negative
Test 2	≥ 490.5	> 250	> 500	negative
Present				
Test 1	≥ 1962	≥ 1500	≥ 1250	negative
Test 2		≥ 1375	≥ 1375	negative

Remarks - Results In test 1, small but statistically significant increases in the frequency of cells with aberrations were observed, predominately in the presence of metabolic activation. The maximum response observed in the presence of metabolic activation was associated with a dose level that induced approximately 50% mitotic inhibition. In the absence of metabolic activation the response was observed at a dose level that exceeded the optimum target level of 50% toxicity. In both cases the response was not

clearly dose-related.

In test 2, the response observed in the presence of S9 was much weaker and was associated with a dose level that slightly exceeded the approximate 50% mitotic inhibition. It only marginally exceeded the in-house historical vehicle control upper limit of 2.0% for exposures with-S9 but was the same as the overall historical maximum for all exposure conditions (2.5%). A small but statistically significant response was observed in the 24-hour continuous exposure at 250 μg/mL, however the aberrations observed were only observed in one of the duplicate cultures and were all break type aberrations. The response was therefore, considered by the study authors to be of little biological relevance.

In summary, a small but statistically significant increase in the frequency of aberrant cells was observed in test 1 in the presence of S9. However, this response was not clearly dose-related and not reproduced in test 2. It was concluded by study authors that the clastogenic activity was occurring at or around the onset of excessive toxicity, thus it had little biological relevance or toxicological significance.

The positive and vehicle controls gave satisfactory responses confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Harlan Laboratories Ltd (2012k)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical Oxygen Demand (BOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Notified chemical		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	2	3	54
15	79	15	91
28	88	28	93

Remarks - Results	The validity criteria were achieved after 14 days for the reference substance (sodium benzoate) as degradation exceeded the pass level of 60%. Examination of the degradation curve for the toxicity control showed that the toxicity control attained in excess of 81% degradation by day 14 of the study thereby confirming that the notified chemical was not toxic to the sewage treatment micro-organisms used in the study. After 28 days the toxicity control had attained 88% degradation. The notified chemical attained 88% degradation after 28 days and, satisfied the 10 day window criterion. Therefore, the notified chemical can be considered as readily biodegradable under the conditions of OECD Guideline 301F.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Firmenich (2011b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi Static.
Species	Zebra fish *(Brachydanio rerio)*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	112 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The range finding test showed that the measured concentration of the test substance was in the range of 80-120% of the nominal concentration. Therefore, the definitive test was performed in semi-static test with renewal every 24 h.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative mortality%*			
Nominal	*Measured*		*24 h*	*48 h*	*72 h*	*96 h*
Control		21	4.8	4.8	4.8	4.8
4.2	3.24	21	0	0	0	9.5
5.46	4.47	21	0	4.8	33	71
7.1	6.06	21	0	38	90	95
9.23	7.79	21	9.5	81	100	100
12	10.42	21	57	95	100	100

LC50	4.22 mg/L at 96 hours, the 95 % confidence limit was 3.91 – 4.56 mg/L (based on measured concentrations by geometric means).
NOEC	< 3.25 mg/L (based on measured concentrations by geometric means).
Remarks – Results	All validity criteria were satisfied and no significant deviations to the protocol were reported. The measured concentration varied from 77-86% of the nominal concentration, therefore, the reported results are based on the measured concentration by geometrical means.
CONCLUSION	The notified chemical is toxic to fish.
TEST FACILITY	GDCM (2013)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static .
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported.

RESULTS

Concentration mg/L	*Number of D. magna*	*Number Immobilised*	
Nominal		*24 h*	*48 h*
Control	20	0	0
1.0	20	0	0
1.8	20	0	0
3.2	20	0	1*
5.6	20	0	20
10	20	6	20

* Single immobilised daphnid was considered due to natural causes rather than a toxic effect given that less than 10% immobilisation was observed.

EC50	4.1 mg/L at 48 hours, the 95 % confidence limit was 3.9 – 4.3 mg/L (based on nominal concentrations).
NOEC	3.2 mg/L.
Remarks - Results	The validity criteria for the test were met.
CONCLUSION	The notified chemical is toxic to aquatic invertebrates.
TEST FACILITY	Harlon (2012l)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*

Exposure Period	72 hours
Concentration Range	Nominal: 62.5, 12.5, 25, 50 and 100 mg/L
Auxiliary Solvent	None
Water Hardness	0.15 mM Ca^{2+} and Mg^{2+}
Analytical Monitoring	HPLC
Remarks - Method	After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported. The test substance (50 mg) was dissolved in 500 mL reconstituted water and stirred ultrasonically for 56 min to give a nominal 100 mg/L stock solution. A series of dilutions was made to give various nominal test solutions.

RESULTS

Biomass		*Growth*	
E_yC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
33	12.5	62	12.5
(95% confidence limits: 29-38)		(95% confidence limits: 57-68)	

Remarks - Results	The validity criteria for the test were met. A concentration decline in measured test concentrations was observed during the range finding test. This was attributed to the absorbance of the test substance to the algal cells. This was further confirmed by the analysis of the uninoculated test samples which showed measured concentrations in the range of 91-95% of the nominal concentrations. However, as the measured test concentrations were within 80-120% of the nominal concentrations it was considered appropriate to calculate the results based on the nominal test concentrations only.
CONCLUSION	The notified chemical is harmful to algae.
TEST FACILITY	Harlon (2012m)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge from domestic sewage treatment plant
Exposure Period	3 hours
Concentration Range	Nominal: 10, 32, 100, 300 and 1000 mg/L Actual: Not measured
Remarks – Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.
RESULTS	
EC50	270 mg/L
Remarks – Results	All validity criteria were satisfied and no significant deviations to protocol were reported.
CONCLUSION	The notified chemical is not expected to be inhibitory to micro-organisms at concentrations < 270 mg/L.
TEST FACILITY	Harlon (2012n)

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