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September 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

2,7-Nonadien-4-ol, 4,8-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 and Energy.

This Public Report is 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

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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/1923	Firmenich Pty Limited	2,7-Nonadien-4-ol, 4,8-dimethyl-	Yes	< 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable liquids (Category 4)	H227 – Combustible liquid
Acute Toxicity (Category 4)	H332 – Harmful if inhaled
Skin Irritation (Category 2)	H315 – Causes skin irritation
Eye Irritation (Category 2A)	H319 – Causes serious eye irritation

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R20: Harmful by inhalation
R38: Irritating to skin
R36: Irritating to eyes

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 3	H402 – Harmful to aquatic life

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

Based on the available information, when used as a fragrance component in a variety of cosmetic and household products at ≤ 1%, 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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - H332 – Harmful if inhaled
  - H315 – Causes skin irritation
  - H319 – Causes serious eye irritation

The above should be used for products/mixtures containing the notified chemical, if applicable, based on the concentration of the notified chemical present and the intended use/exposure scenario.

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

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:
  - Enclosed, automated processes, where possible
  - Ventilation system, including local exhaust ventilation

- 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 contact with skin and eyes
  - Avoid breathing of vapours and mists

- 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, coveralls
  - Respiratory protection in case of poor ventilation

  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 of 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.

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 1% in cosmetic products and house hold products.

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

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 cosmetic and household products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical as 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.

(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(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: other names, analytical data, degree of purity, impurities and additives/adjuvants.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

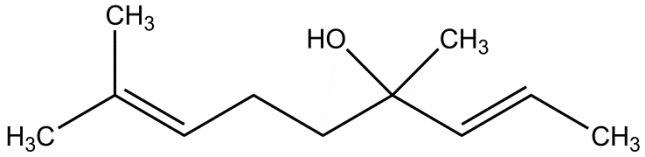
MARKETING NAME(S)
2,7-Nonadien-4-ol, 4,8-dimethyl-

CAS NUMBER
103983-77-3

CHEMICAL NAME
2,7-Nonadien-4-ol, 4,8-dimethyl-

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

STRUCTURAL FORMULA



MOLECULAR WEIGHT
168.28 Da

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

3. COMPOSITION

DEGREE OF PURITY
90–100%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -80 °C	Measured
Boiling Point	215 °C at 101.4 kPa	Measured
Density	867 kg/m^3 at 20 °C	Measured
Vapour Pressure	5.8 × 10^{-3} kPa at 20 °C 11 × 10^{-3} kPa at 25 °C	Measured
Water Solubility	0.667 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Stable at pH > 5	Measured*
Partition Coefficient (n-octanol/water)	log Pow = 3.8	Measured
Surface Tension	44.3 mN/m at 20 °C (90% concentration)	Measured
Adsorption/Desorption	log Koc = 2.9	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	87 °C (pressure unknown)	Measured
Autoignition Temperature	240 °C at 101.8 kPa	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties.

*In-house method, full study report not available.

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 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. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Flammable Liquids (Category 4)	H227 – Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia in its pure form or as a component in a fragrance formula (at a concentration ≤ 1%).

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 RECIPIENTS
Firmenich Pty Limited

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in either its pure form or as a component of fragrance preparations containing the notified chemical (at ≤ 1% concentration). The notified chemical will be imported and distributed in lacquered drums of 180 (typical size), 100, 50, 25, 10 or 5 kg in size. They will be transported by road to the warehouse for storage and then distributed to reformulation sites. The notified chemical may be transported directly to the customer's facilities from the port of entry. End-use products 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 at ≤ 1% concentration.

OPERATION DESCRIPTION
The procedures for incorporating the imported preparations (in pure form or at ≤ 1% concentration) into end-use products will likely vary depending on the nature of the cosmetic and personal care/household cleaning products formulated, and may involve both automated and manual transfer steps. It is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed/contained environment, followed by automated filling (using sealed delivery systems) of the reformulated end-use products into containers of various sizes.

The end-use products containing the notified chemical (at ≤ 1% 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
Maintenance	4	2
Quality Control	0.5	1
Packaging	4	2
Salon Workers	Unspecified	Unspecified
Cleaners	Unspecified	Unspecified

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical at ≤ 100% concentration or as a component of the imported preparations (at a concentration of ≤ 1%), only in the event of accidental rupture of containers. The primary work activity undertaken by the workers will be loading and off-loading of containers. Incidental exposure to the notified chemical may occur via skin or eye during the clean-up of accidental spills.

Formulation of end use products
During reformulation, dermal, ocular and potentially inhalation exposure of workers to the notified chemical (in pure form) may occur during: weighing and transfer stages, equipment preparation, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of mechanical exhaust ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as gloves, respirator, eye protection and protective clothing.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at ≤ 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hairdressers, workers in beauty salons) or in the cleaning industry. Such professionals may use 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 a concentration ≤ 1%) through the use of the household cleaning products, perfumes and both 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 product categories in which the notified chemical may be used are shown in the following table (SCSS, 2012; Cadby *et al*., 2002). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. An adult bodyweight of 64 kg was used for calculation purposes. Based on absence of dermal absorption data on the notified chemical, a dermal absorption of 100% was assumed for the notified chemical.

Cosmetic products (Dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	1	1	1.2219
Face cream	1,540	1	1	0.2406
Hand cream	2,160	1	1	0.3375
Fragrances	750	1	1	0.1172
Deodorant (non-spray)	1,500	1	1	0.2344
Shampoo	10,460	1	0.01	0.0163
Hair conditioner	3,920	1	0.01	0.0061
Shower gel	18,670	1	0.01	0.0292
Hand wash soap	20,000	1	0.01	0.0313
Hair styling products	4,000	1	0.1	0.0625
Total				**2.2970**

C = concentration (%); RF = Retention Factor
Daily Systemic Exposure = (Amount × C × RF x dermal absorption)/body weight

Hair spray (inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	1	20	1	20	50	1	10	**0.0332**

Total Daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]
Note - conversion factors of 0.1 [to account for C/Bioavailability as a % and unit conversion (g to mg) ((1/100 × 1/100) × 1,000)] and 1,440 [to account for mins to day conversion, i.e. 1440 mins/day]

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	1	0.95	10	0.0341
Fabric softener	90	1	0.95	10	0.0134
Total					**0.0475**

Daily Systemic Exposure = (Amount × C × PR × PT)/body weight

Household products (Direct dermal exposure – from wearing clothes)

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	1	1,980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1	1,980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1	1,980	1	0.01	0.007	0.0217
Total							**0.0245**

Daily Systemic Exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale factor × dermal absorption)/body weight

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 2.4011 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 conservative hair spray inhalation exposure assessment parameters, (in particular assuming an airspace volume of 2 m^3), and the aggregate exposure form the 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 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC 50 = 4.84 (4.29–5.38) mg/L/4 hours for females only; harmful
Skin irritation (in vitro)	irritating
Skin irritation (in vitro)	non-corrosive
Eye irritation (in vitro)	no prediction of eye irritation can made
Rabbit, eye irritation	irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution

No information on the toxicokinetics of the notified chemical was provided. For dermal absorption, molecular weights between 100 and 500 Da are favourable for absorption (ECHA, 2014). Dermal uptake is likely to be moderate to high if the water solubility is between 100-10,000 mg/L and log P values between 1 and 4 also favour dermal absorption (ECHA, 2014). Based on the water solubility (0.667 g/L at 20 °C), partition coefficient (log Pow = 3.8) and the low molecular weight (168.28 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are possible. The notified chemical may also be absorbed across the respiratory tract if inhaled.

Acute toxicity
The notified chemical was found to have low acute toxicity in rats via the oral and dermal routes.

The notified chemical was considered to be harmful via the inhalation route. All the test animals exposed to 3.25–5.05 mg/L of test substance for 4 hours showed signs of toxicity and 4 out of 10 animals in Group 1 and 2 out of 5 animals in Group 2 had to be sacrificed for ethical reasons. The LC50 was reported to be 4.84 mg/L/4 hours.

Irritation
Evidence of irritation was observed in an in vitro skin irritation study using the Reconstructed Human Epidermis Model. The notified chemical was non-corrosive to the skin under the conditions of an in vitro Skin Corrosion - Human Skin Model Test.

No prediction could be made on the eye irritation potential of the notified chemical in an in vitro eye irritation study using the Bovine Corneal Opacity and Permeability (BCOP) Assay. The notified chemical was irritating to the eyes when tested in rabbits.

Sensitisation
The notified chemical showed no evidence of reactions indicative of skin sensitisation when challenged at 100% in a guinea pig maximisation test.

Repeated dose toxicity
In a 28 day repeat dose study by oral gavage, rats were administered the notified chemical at doses of 100, 300 or 1,000 mg/kg bw/day. The findings in the study were considered by the study authors to be adaptive, non-adverse and most of them had evidence of reversibility after 2 weeks of recovery for all tested animals. Hence the No Observed Adverse Effect Level (NOAEL) was established as 1,000 mg/kg bw/day in this study.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study and non-clastogenic in an in vitro mammalian chromosome aberration test.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Acute Toxicity (Category 4)	H332 – Harmful if inhaled
Skin Irritation (Category 2)	H315 – Causes skin irritation
Eye Irritation (Category 2A)	H319 – Causes serious eye irritation

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R20: Harmful by inhalation
R38: Irritating to skin
R36: Irritating to eyes

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Formulation of end use products
Exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during blending operations, quality testing, equipment cleaning and maintenance. The notified chemical is a skin and eye irritant. In addition, harmful effects following inhalation and/or repeated exposure to the notified chemical is possible. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

Provided that control measures are in place to minimise worker exposure, including the use of automated processes and personal protective equipment (PPE), such as impervious gloves, coveralls, safety glasses and

respiratory equipment with gas filter (in cases where there is inadequate ventilation) the risk to the health of workers during the reformulation of the notified chemical is not considered to be unreasonable.

Beauty care and cleaning professionals
Cleaners and beauty care professionals will handle the notified chemical at ≤ 1% concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than 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.

6.3.2. Public Health
Members of the general public may experience repeated exposure to the notified chemical through the use of cosmetic and household products containing the notified chemical at ≤ 1% concentration.

Local effects
The notified chemical is harmful if inhaled and has the potential to cause irritation to the skin and eyes. However, these effects are not expected from the use of products containing the notified chemical at proposed concentrations in cosmetic and household products.

Systemic effects
Members of the public may experience repeated exposure to the notified chemical through the use of the cosmetic and household products (containing the notified chemical at ≤ 1% concentration).

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 2.4011 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 1,000 mg/kg bw/day, as established by the study authors in a 28-day repeated dose toxicity study on the notified chemical. Using the abovementioned NOAEL, a MoE of 416 was estimated. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure; 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 as a fragrance component in a variety of cosmetic and household products at ≤ 1% 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 neat or as a component of fragrance formulations, for reformulation into finished cosmetic formulations and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. It is estimated by the notifier that a maximum of 0.1% of the import volume of the notified chemical (or up to 1 kg) may be released from accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail and use. Wastes containing the notified chemical generated during reformulation include equipment wash water, empty import containers and spilt materials. These are expected to be collected and recycled during subsequent blending processes. Empty import containers are expected to be recycled or disposed of through licensed waste management services.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic formulations and household products.

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated by the notifier that a maximum of 0.003% of the import volume of the notified chemical (or up to 30 g), may remain in end-use containers once the consumer products are used up. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. Based on the results of a ready biodegradability study, the notified chemical is considered readily biodegradable (78.6% in 28 days). For details of the environmental fate study, please refer to Appendix C. Based on its surfactant properties release to surface waters is unlikely to occur, as partitioning to sludge and sediment is expected under environmental pH. The notified chemical is not expected to bioaccumulate due to its surfactant properties and ready biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile from water (vapour pressure = 5.8×10^{-3} kPa at 20 °C) and may slowly volatilise to air during sewage treatment. The half-life of the notified chemical in air is calculated to be < 1 h, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation, when sewage sludge is used for soil remediation. The notified chemical may also be applied to land when disposed of to landfill as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

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:	0.606	µg/L
PEC - Ocean:	0.061	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 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 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the 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*
Fish Toxicity	96 h LC50 = 11.3 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 21 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 55 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 250 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be harmful to aquatic life. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as 'Acute Category 3; Harmful to aquatic life'. Based on the acute toxicity, ready biodegradability and low bioaccumulation potential of the notified chemical, it is not formally classified under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for fish. A safety factor of 100 was used given acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	11.30	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	113	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.606	113	**0.005**
Q – Ocean	0.061	113	**0.001**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. The notified chemical is considered readily biodegradable, and is expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household 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 < -80 °C

Method OECD TG 102 Melting Point/Melting Range.
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks It was measured by applying a storage experiment in the freezer.
Test Facility WIL Research Europe B.V. (2015a)

Boiling Point 215 °C at 101.4 ± 0.1 kPa

Method OECD TG 103 Boiling Point.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Differential scanning calorimetry technique was used.
Test Facility WIL Research Europe B.V. (2015a)

Density 867 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks A pycnometer was used.
Test Facility WIL Research Europe B.V. (2015a)

Vapour Pressure 5.8×10^{-3} kPa at 20 °C
11×10^{-3} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks Isothermal thermogravimetric effusion method was used.
Test Facility WIL Research Europe B.V. (2015b)

Water Solubility 0.667 g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Slow-stirring flask method.
Test Facility WIL Research Europe B.V. (2015c)

Hydrolysis as a Function of pH Stable at pH > 5

Method In-house method.

The notified chemical was dissolved in buffers at pH 2, 5, 7, 8.5, and 12 to reach concentrations in the range of 200–300 ppm. The mixtures were then incubated at 40 °C. Small aliquots of the test solutions were extracted using an organic solvent containing a hydrocarbon standard on a regular basis throughout the test. The extracts were analysed by gas chromatography.

pH	*T (°C)*	*$t_{½}$ (days)*
2	40	<< 1
5	40	15
7	40	> 365
8.5	40	> 365
12	40	> 365

Remarks The notified substance is hydrolytically stable at pH > 5; unstable at pH ≤ 5
Test Facility Firmenich

Partition Coefficient (n-octanol/water) log Pow = 3.8

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC and UPLC methods.
Test Facility	WIL Research Europe B.V. (2015d)

Surface Tension 44.3 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Ring method.
Test Facility	WIL Research Europe B.V. (2015e)

Adsorption/Desorption log K_{oc} = 2.9

Method	OECD TG 121 Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) EC Council Regulation No 440/2008 C.19 Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
Remarks	HPLC and UPLC methods.
Test Facility	WIL Research Europe B.V. (2015f)

Flash Point 87 °C (pressure unknown)

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	It was measured according to the ASTM D93c method using an Eraflash flash-point tester.
Test Facility	WIL Research Europe B.V. (2015a)

Autoignition Temperature 240°C at 101.75–101.76 kPa

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	WIL Research Europe B.V. (2015c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/RccHan®:WIST albino
Vehicle	Corn oil
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	300	0
2	3 F	300	0
3	3 F	2,000	0
4	3 F	2,000	0

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No clinical signs were noted in any animal dosed at 300 mg/kg. Clinical signs were seen in some animals dosed at 2,000 mg/kg: 3 showed piloerection, 2 showed decreased activity, 1 showed unsteady gait and one showed hunched posture. These observation were first observed on day1 and all disappeared by day 3.
Effects in Organs	No abnormalities were observed in any animal at the macroscopic examination.
Remarks - Results	Body weight gain was normal.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Huntingdon Life Sciences (2015)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	None
Type of dressing	Semi-occlusive.
Remarks - Method	GLP Certificate. No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 per sex	2,000	0
2	4 per sex	2,000	0

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No signs of dermal irritation were observed.

Signs of Toxicity - Systemic	No signs of systemic toxicity were observed.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	Animals showed expected body weight gains, except that two females animals showed body weight loss during the first week but expected body weight gain during the second week.

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

TEST FACILITY Envigo Research Limited (2015)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 403 Acute Inhalation Toxicity.
EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation).

Species/Strain	Rat/RccHan™:WIST
Vehicle	None
Method of Exposure	Oro-nasal exposure
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	3.26–3.43 µm (57.6–61.2% < 4 µm)
Remarks - Method	GLP Certificate. Only one particle size determination was performed during the characterisation phase of the study due to a technician oversight. Test atmospheres were generated for a total of 10, 12 and 21 minutes for groups 1, 2 and 3 respectively prior to animal insertion to ensure that test substance concentrations were achieved. Due to the number of deaths observed during the first exposure group, it was decided not to expose further groups of male animals.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <units>*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	21.9	5.05 ± 0.12	1 M, 3 F
2	5 F	11.9	3.25 ± 0.23	0
3	5 F	17.2	4.62 ± 0.08	2 F

LC50	5.23 (4.45–6.01) mg/L/4 hours for all animals* 5.18 (3.98–6.38) mg/L/4 hours for males only* 4.84 (4.29–5.38) mg/L/4 hours for females only *These results were calculated on the assumption that all male animals would have survived at the two lower dose levels.
Signs of Toxicity	In group 1, decreased respiratory rate was observed in all animals during exposure and there were occasional instances of laboured respiration. On removal from the chamber, all animals showed decreased or increased respiratory rate. Occasional instances of laboured respiration, ataxia and coma and isolated instances of lethargy and exophthalmos were also observed. Little or no changes in the condition of the animals were observed one hour post exposure. At a further health check approximately 158 minutes post exposure it was considered appropriate to humanely kill the 4 comatose animals as they were not expected to survive. On the day after exposure, all surviving animals showed increased or decreased respiratory rate, noisy respiration, hunched posture and pilo-

erection. One female animal showed laboured respiration. All surviving animals appeared normal on day 7 post exposure.

In group 2, decreased respiratory rate was observed in all animals during exposure and there was an isolated instance of laboured respiration. One hour post-exposure on removal from the chamber, all animals showed decreased respiratory rate and there was isolated occurrence of ataxia.

On the day after exposure, all animals showed increased respiratory rate, hunched posture and pilo-erection. All animals appeared normal on day 3 post exposure.

In group 3, decreased respiratory rate was observed in all animals during exposure and there were occasional instances of laboured respiration. One hour post-exposure on removal from the chamber, all animals showed decreased respiratory rate. There were occasional instances of ataxia and laboured respiration and isolated occurrences of coma and prostration.

On the day after exposure, one animal was dead. All surviving animals showed increased or decreased respiratory rate, hunched posture and pilo-erection. There were occasional instances of red/brown staining around the eyes and snout. One animal showed laboured respiration, dehydration, pallor of the extremities, prostration, ptosis and pilo-erection. Based on these observations, this animal was killed as it was not expected to survive. All surviving animals appeared normal on day 6 post exposure.

The body weight for all animals decreased on day 1 and increased at the end of observation period.

Effects in Organs	In group 1, the two males and three females that died during the study showed dark patches on the lungs. All other animals appeared normal at necropsy. In group 2, all animals appeared normal at necropsy. In group 3, the two dead animals during the study showed dark patches on the lungs and dark substances in the small intestine. All other animals appeared normal at necropsy.
Remarks - Results	The deaths observed during the study were attributed to systemic toxicity based on the observations during the study and at necropsy.

CONCLUSION The notified chemical is harmful via inhalation.

TEST FACILITY Harlan Laboratories Ltd (2015a)

B.4. Irritation – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method

Vehicle	None
Remarks - Method	GLP Certificate. Minor deviations were not considered to affect the purpose or integrity of the study.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0868 ± 0.011	100*	1.3
Test substance	0.0086 ± 0.015	9.9	1.8
Positive control	0.093 ± 0.012	10.7	1.4

OD = optical density; SD = standard deviation

*The mean % viability of the negative control tissue is set at 100%.

Remarks - Results	The test substance did not reduce MTT as the MTT solution containing it did not become blue. The mean concentration of inflammatory mediator IL-1α in the culture medium retained from the test substance treated tissues was 164.375 pg/mL. The quality criteria required for acceptance of results in the test were satisfied.
CONCLUSION	The notified chemical was irritating to the skin under the conditions of the test.
TEST FACILITY	Harlan Laboratories Ltd (2015b)

B.5. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 In vitro Skin Corrosion - Human Skin Model Test EC Council Regulation No 440/2008 B.40 BIS. In vitro Skin Corrosion - Human Skin Model Test
Vehicle	None
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Exposure period: 3 minutes

Test material	*Mean OD_{562} of duplicate tissues*	*Relative mean Viability (%)*
Negative control	2.429 ± 0.107	100*
Test substance	2.414 ± 0.163	99.4
Positive control	0.107 ± 0.030	4.4

OD = optical density; SD = standard deviation

Exposure period: 60 minutes

Test material	*Mean OD_{562} of duplicate tissues*	*Relative mean Viability (%)*
Negative control	2.369 ± 0.016	100*
Test substance	1.080 ± 0.200	45.6
Positive control	0.093 ± 0.018	3.9

OD = optical density
*The mean % viability of the negative control tissue is set at 100%.

Remarks - Results	The test substance did not reduce MTT as the MTT solution containing it did not become blue. The test substance did not have the potential to cause colour interference as the solution containing it did not turn coloured. The quality criteria required for acceptance of results in the test were satisfied.
CONCLUSION	The notified chemical was non-corrosive to the skin under the conditions of the test.
TEST FACILITY	Envigo Research Limited (2016a)

B.6. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical

METHOD: OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage

Vehicle: None

Remarks - Method: GLP Certificate.
Minor deviations were not considered to affect the purpose or integrity of the study.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	1.3	0.037	1.9
*Test substance**	7.0	0.449	13.7
*Positive control**	28.3	1.418	49.6

SD = Standard deviation; IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results: The corneas treated with the test substance were slightly cloudy post treatment and post incubation. The corneas treated with the negative control were clear post treatment and post incubation. The corneas treated with the positive control were cloudy post treatment and post incubation.

The positive and negative acceptance criteria were satisfied.

CONCLUSION: No prediction of eye irritation can made for the notified chemical under the conditions of the test.

TEST FACILITY: Harlan Laboratories Ltd (2015c)

B.7. 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).
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).

Species/Strain: Rabbit/New Zealand White

Number of Animals: 3 M

Observation Period: 14 days

Remarks - Method: GLP Certificate.
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			
Conjunctiva: redness	2	2	2	2	< 14 d	0
Conjunctiva: chemosis	1.7	1.7	1.3	2	< 14 d	0
Conjunctiva: discharge	1.3	1.3	1.0	2	< 14 d	0
Corneal opacity	1	1	1	1	< 7 d	0
Iridial inflammation	1	1	1	1	< 7 d	0

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

Remarks - Results: Scattered or diffuse corneal opacity was observed in all treated eyes at the 24, 48 and 72-hour observations.

Iridial inflammation was observed in all treated eyes at the 1, 24, 48 and

72-hour observations.

Moderate conjunctival irritation was observed at the 1, 24 and 48-hour observations. At the 72-hour observation, moderate conjunctival irritation was observed in two treated eyes with minimal conjunctival irritation noted in one treated eye. At the 7-day observation, minimal conjunctival irritation was observed in all treated eyes. All effects disappeared at the 14-day observation. The body weight gain was normal for all animals.

CONCLUSION The notified chemical is irritating to the eye.

TEST FACILITY Envigo Research Limited (2016b)

B.8. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation - Magnusson and Kligman method.
EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson and Kligman method.

Species/Strain Guinea pig/Dunkin-Hartley

PRELIMINARY STUDY Maximum Non-irritating Concentration: 100%
intradermal: 10%, 20%, 50% and 100%
topical: 10%, 20%, 50% and 100%

MAIN STUDY 1

Number of Animals Test Group: 10 F Control Group: 5 F

INDUCTION PHASE Induction Concentration:
intradermal: 10%
topical: 100%

Signs of Irritation Dryness of the skin was observed in all animals in the test group after the second induction.

CHALLENGE PHASE

1st challenge topical: 100%

2nd challenge topical: 100%

MAIN STUDY 2

Number of Animals Test Group: 10 F Control Group: 5 F

INDUCTION PHASE Induction Concentration:
intradermal: 10%
topical: 100%

Signs of Irritation Discrete erythema was observed in 4 animals in the test group after the first induction. Dryness of the skin was observed in all animals in the test group and three animals in the control group after the second induction.

CHALLENGE PHASE

challenge topical: 100%

Vehicle Olive oil for the intradermal injections and liquid paraffin for the topic applications

Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.

Remarks - Method Minor deviations were not considered to affect the purpose or integrity of the study.

As it appeared that the vehicle was having some impact on the results in the first test, a second test was conducted with 5 new control animals and 10 treated animals in the same experimental conditions except that no second challenge was conducted.

RESULTS

Test 1

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*

		1st challenge		2nd challenge	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	0%	1/10	0/10	1/10	0/10
	100%	4/10	0/10	1/10	0/10
Control Group	0%	0/5	0/5	0/5	0/5
	100%	0/5	0/5	0/5	0/5

Test 2

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	0%	0/10	0/10
	100%	0/10	0/10
Control Group	0%	0/5	0/5
	100%	0/5	0/5

Remarks - Results: The body weight gain for all animals was normal. No mortality occurred during the main study.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: Phycher Bio Development (2016)

B.9. 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/CD
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 14 days
Vehicle: Corn oil
Remarks - Method: GLP Certificate.
Minor deviations were not considered to affect the purpose or integrity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	100	0
mid dose	5 per sex	300	0
high dose	5 per sex	1,000	0
control recovery	5 per sex	0	0
high dose recovery	5 per sex	1,000	0

Mortality and Time to Death
There were no unscheduled deaths during the study.

Clinical Observations
There were no adverse clinical signs that were considered related to treatment. Salivation was observed in the high and mid dose groups and chin rubbing was noted in one female animal in the high dose group.

Sensory reactivity, grip strength, motor activity and food consumption (with variation but no dose response) did not show any response to treatment. In week 3, an increase in water consumption was observed for animals in the high dose group. Females in the high dose group gained more body weight than the controls with statistical significance; however, this effect was not noted for the reminder of the treatment period or for males.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Overall, there were no adverse treatment-related changes in the haematology parameters.

Statistically significant higher platelet numbers in males in low, mid and high dose groups than controls, which has slightly lower value, were observed in the haematological examination after 28 days of treatment. A similar effect was not noted in females. The effects disappeared in the high dose group after 2 weeks of recovery.

Statistically significant lower mean cell haemoglobin concentration than controls was observed in males in the mid and high dose groups. There was no dose relationship or an effect of any of the other red cell indices. The effects disappeared in the high dose group after 2 weeks of recovery.

Two females at the high dose group had shorter activated partial thromboplastin times compared with the controls with no statistically significant differences. The effects disappeared after 2 weeks of recovery.

After the two weeks of recovery period, males in the high dose group showed decreased haemoglobin concentration and erythrocyte counts and increased red cell distribution width, when compared with controls, with statistical significance. As these effects did not appear after 28 days of treatment, these variations were not considered related to the treatment.

Statistically significant lower mean plasma urea concentration than controls was observed in females in the high dose group. The effects disappeared in the high dose group after 2 weeks of recovery.

In males in the high dose group, higher albumin total protein concentrations compared with controls were observed and it led to a lower mean albumin-globulin ratio with statistical significance. After 2 weeks of recovery, albumin and total protein values were comparable to controls; however, the mean albumin-globulin ratio remained statistically significant lower than controls in this group. A statistically significantly lower mean albumin-globulin ratio was noted at the end of the recovery period for females; however, no such finding was noted after 28 days of treatment.

Statistically significant increases in plasma cholesterol and triglyceride concentrations were observed in females in the high dose group. This was caused predominantly by the result of high values in one female. After 2 weeks of recovery, the effect for triglyceride concentrations disappeared while cholesterol concentrations improved; however, they remained marginally high with statistical significance. Plasma cholesterol concentrations were also statistically significantly higher in 4 out of 5 males in the high dose group and this effect was not observed at the end of 28 days of treatment.

In males in the high dose group, decreased chloride and increased calcium concentrations were observed with statistical significance. After 2 weeks of recovery, the effect on calcium concentration was still noted with the magnitude of difference from the controls being reduced, suggesting partial recovery of this electrolyte change. In addition, a statistically significantly increased plasma phosphorus concentrations and decreased plasma chloride concentrations without statistical significance were still noted at the end of the recovery period for females in the high dose group.

After the two weeks of recovery period, males and females in the high dose group showed lower alkaline phosphatase activities, when compared with controls, with statistical significance for males only. As these effects did not appear after 28 days of treatment, these variations were not considered related to the treatment.

Urinalysis after 28 days of treatment showed statistically significantly lower urinary pH for females in low-, mid- and high-dose groups and males in the high dose group when compared with control. Specific gravity was statistically significantly higher than the control group for females in all treated groups.

When compared with controls, statistically significant higher urinary total sodium and chloride were reported in males in the high dose group. Total sodium was statistically significantly lower than controls for all treatment groups without dose relationship and thus the effect was not considered to be related to treatment.
Higher than control urinary glucose was noted for all treated male groups, with statistical significance for the

high dose group. However, the control mean was negatively impacted by low values in two animals. The highest values for urinary glucose were observed in males in the mid- and high-dose groups, with the magnitude of change between these groups showing a dose-related response. The study authors considered this small increase in total glucose in few animals was likely to be related to treatment but was not adverse.
Microscopic evaluation showed the unidentified crystals/clumps of material in the sediment of two males in each of the mid- and high-dose groups. No such material was found in any animals after two weeks of recovery.

After two weeks of recovery, urinary pH in males and females and total sodium and chloride concentrations in males appeared fully recovered. Specific gravity remained slightly high in two females and glucose remained slightly high in males without statistical significance. Specific gravity was statistically significantly low in males, however, the change was considered unrelated to the treatment in the absence of a similar difference at the end of the treatment period.

Effects in Organs
Body weight adjusted liver weight was higher than the control in both sexes in the high dose group. In the recovery group only males showed a statistically significant liver weight increase. Higher than control body weight adjusted kidney weights were noted in males with statistical significance in the mid dose group and in females in the high dose group. These effects fully recovered after 2 weeks.

There were no macroscopic abnormalities related to treatment found at scheduled termination after 4 weeks of treatment or after 2 weeks of recovery.

Changes related to treatment were observed in the liver, kidneys and thyroids, mainly in the males. Centrilobular hypertrophy in liver was noted in 1 female in the mid dose group, and in 5 males and 3 females in the high dose group. Following 2 weeks of recovery, findings related to treatment were still noted in the liver of 1 male in the high dose group. There was a complete recovery for the females and partial recovery for males.

Minimal hyaline droplets in kidneys were noted in 3 males in each of the mid- and high- dose groups. Minimal follicular cell hypertrophy was noted in all male groups including controls, with 4/5 animals affected in the mid and high dose groups. The changes noted in the low dose group were considered unrelated to treatment as the incidence was just slightly above control levels.

Changes noted in the thyroids and kidneys of males in the mid- and high-dose groups disappeared after 2 weeks of recovery. All other histological changes were considered unrelated to treatment.

Remarks – Results
Liver as a target organ showed adaptive changes such as increased cholesterol levels, increased liver weights and centrilobular hypertrophy. The follicular cell hypertrophy in the thyroid might be linked to enzymatic induction in the liver which was a well-recognised rodent specific phenomenon. As it is irrelevant to humans, this was considered secondary to liver effects and not to be adverse. There might be a causal relationship between the liver and thyroid changes based on the effects observed in mid- and high-dose groups.

The accumulation of hyaline droplets is indicative of alpha2μ-globulin nephropathy, which is specific to mature male rats. This finding was linked to a slight increase of the kidney weights. However, as hyaline droplet production is irrelevant to humans, this was not considered be adverse.

The findings in the study were considered by the study authors to be adaptive and most of them showed evidence of reversibility after 2 weeks of recovery.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1,000 mg/kg bw/day in this study, based on none of findings seen at the high dose group were considered adverse by the study authors in this study.

TEST FACILITY Envigo CRS Limited (2015)

B.10. 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. Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	A rat liver homogenate metabolising system (10% liver S9 in standard co-factors)
Concentration Range in Main Test	*S. typhimurium*: TA98 and *E. coli*: WP2uvrA without metabolic activation and all tester strains with S-9 mix: 0, 0.5, 1.5, 5, 15, 50, 150 and 500 µg/plate *S. typhimurium*: TA1535, TA1537, TA100 without metabolic activation: 0, 0.15, 0.5, 1.5, 5, 15, 50 and 150 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	GLP Certificate. No protocol deviations. The dose range used for the main test was determined by the results of the preliminary test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	≥ 150			
Test		≥ 150	> 500	negative
Present	≥ 500			
Test		≥ 500	> 500	negative

Remarks - Results	There were no toxicologically significant increases in the frequency of revertant colonies recorded for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation in both experiments. The positive and negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Harlan Laboratories Ltd (2015d)

B.11. 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 phenobarbitone/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks - Method	GLP Certificate. No protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 13.13, 26.25, 52.5*, 105*, 157.5*, 210*	4	24
Test 2	0*, 6.56, 13.13, 26.25*, 52.5*, 78.75*, 105, 210	24	24

Present			
Test	0*, 26.25, 52.5, 105*, 131.25,157.5*, 210*, 420	4	24

*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	> 105.19			
Test 1		≥ 210	> 210	negative
Test 2		> 78.75	> 210	negative
Present	> 210.38			
Test		> 210	> 420	negative

Remarks - Results

The test substance did not induce any statistically significant increases in the frequency of cells with chromosome aberrations either in the absence or presence of metabolic activation.

The test substance did not induce a statistically significant increase in the number of polyploid cells (no incidence of endoreduplication was noted) at any dose level in either of the exposure groups.

The positive and vehicle control values confirmed 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 (2015e)

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
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Toxicity control*		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*	*Day*	*% Degradation*
7	53.2	7	53.8	7	70.9
14	74.2	14	73.7	14	78.8
21	76.4	21	82.7	21	81.4
28	78.6	28	87.9	28	82.5

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, surpassed the threshold level of 60% by 4 days (61.9%). Therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 2 days (28.2%; 87.9% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 78.6%. As the test substance is surface active, the 10-day window is not applicable. Therefore, the test substance is considered to be readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Safety Evaluation Center (2015)

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	*Danio rerio* (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	136 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*

Control	Control	10	0	0	0	0
3	2.79	10	0	0	0	0
4.5	4.42	10	0	0	0	0
6.7	6.68	10	0	0	0	0
10	10.1	10	0	0	0	20
15	15.4	10	0	10	100	100

LC50	11.30 mg/L (95% CI 10.20–12.51 mg/L) at 96 hours.
NOEC	Not determined
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 96 h test period. The actual concentrations of the test substance were measured at 0, 24, 72 and 96 hours during the 96 h test period. As measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 96 h LC50 for fish was determined to be 11.30 mg/L (95% CI 10.20–12.51 mg/L), based on nominal concentrations.

CONCLUSION The notified chemical is considered to be harmful to fish.

TEST FACILITY Safety Evaluation Center (2016)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
10	9.44	20	0	0
17	15.6	20	0	20
30	30.0	21	29	95
52	47.5	20	85	100
100	91.8	20	100	100

EC50	21 mg/L (95% CI 18–23 mg/L) at 48 hour
NOEC	Not determined
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 48 h test period. The actual concentrations of the test substance were measured at the start and every 24 hours during the 48 h test period. As measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 48 h EC50 for daphnids was determined to be 21 mg/L (95% CI 18–23 mg/L), based on nominal concentrations.

CONCLUSION The notified chemical is considered to be harmful to aquatic invertebrates.

TEST FACILITY WIL Research Europe B.V. (2015h)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test – Static.
Species	*Pseudokirchneriella subcapitata* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 0.032–100 mg/L Actual: 0.52–82 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
17	3.2	55	3.2

Remarks - Results	During the test, the incubation temperature was briefly outside of the prescribed 21–24 °C range (20.6 °C for 50 minutes). However, this was not deemed to have significantly impacted the validity or integrity of the test. All other validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at 0, 24 and 72 hours during the 72 h test period. As measured concentrations deviated from the nominal concentrations by the end of the test, the time weighted average (TWA) concentrations were calculated. The 72 h EC50 for algae was determined to be 55 mg/L (95% CI 47–63 mg/L), based on TWA concentrations. The 72 h NOEC was determined to be 3.2 mg/L (95% CI 8.9–17 mg/L) based on TWA concentrations.
CONCLUSION	The notified chemical is considered to be harmful to algae.
TEST FACILITY	WIL Research Europe B.V. (2015i)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 46–1,000 mg/L Actual: Not determined
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. 3,5-Dichlorophenol was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.
RESULTS	
IC50	250 mg/L (95% Ci 240–270 mg/L) at 3 hours
NOEC	100 mg/L
Remarks – Results	The temperature measurement was started 30 minutes after the start of the

	test, and was based on the fume hood temperature sensor instead of media measurements. However, this was not deemed to have significantly impacted the validity or integrity of the test. All other validity criteria for the test were satisfied. The 3 h IC50 and NOEC were determined to be 250 mg/L (95% CI 240–270 mg/L) and 100 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The notified chemical is not considered to be inhibitory to microbial respiration.
TEST FACILITY	WIL Research Europe B.V. (2015j)

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