File No: STD/1617
STD/1618

October 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

STD/1617: Cyclohexanol, 4-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-
STD/1618: Cyclohexanol, 5-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-

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

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
STD/1617	International Flavours & Fragrances (Australia) Pty Ltd	Cyclohexanol, 4-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-	Yes	≤ 5 tonnes per annum	Fragrance ingredient
STD/1618	International Flavours & Fragrances (Australia) Pty Ltd	Cyclohexanol, 5-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-	Yes	≤ 5 tonnes per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemicals are 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*
Skin Corrosion/Irritation (Category 2)	H315 – Causes skin irritation
Serious Eye Damage/Eye irritation (Category 2A)	H319 – Causes serious eye irritation

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*
Chronic (Category 2)	H411 - Toxic to aquatic life with long lasting effects

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

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemicals should be classified as follows:
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Serious Eye Damage/Eye irritation (Category 2A): H319 – Causes serious eye irritation

The above should be used for products/mixtures containing the notified chemicals, if applicable, based on the concentration of the notified chemicals present.

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 chemicals during reformulation processes:
  - Enclosed, automated processes, where possible
  - Good general ventilation, including local exhaust ventilation if possible

- 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 chemicals during reformulation processes:
  - Avoid contact with skin and eyes

- 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 chemicals during reformulation processes:
  - Coveralls, impervious gloves, goggles

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

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

- If products and mixtures containing the notified chemicals 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.

Disposal

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

Storage

- The handling and storage of the notified chemicals 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 chemicals 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 chemicals 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 chemicals, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemicals are 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 concentration of the two notified chemicals combined exceeds or is intended to exceed 3% in end-use products

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemicals has changed from fragrance ingredient, or is likely to change significantly;
- the amount of chemicals being introduced has increased, or is likely to increase, significantly;
- the chemicals have begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemicals 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 product containing the notified chemicals 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)
International Flavours and Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year)
Standard: Chemical other than polymer (more than 1 tonne per year) (reduced fee notifications): group assessment

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH, dissociation constant, genotoxicity *in vivo* and bioaccumulation

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China

2. IDENTITY OF CHEMICAL

The notified chemicals are part of the same reaction mixture (two isomers).

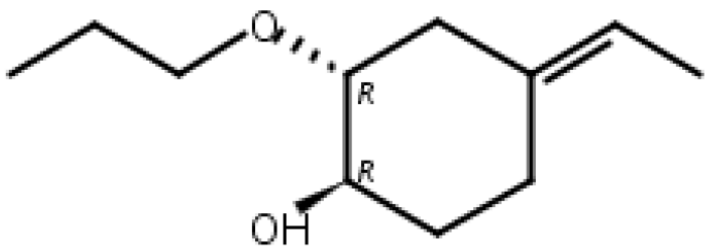
MARKETING NAME(S)
Veraspice (isomer mixture containing the notified chemicals)

CAS NUMBER
STD/1617: 2101609-63-4
STD/1618: 2101609-62-3

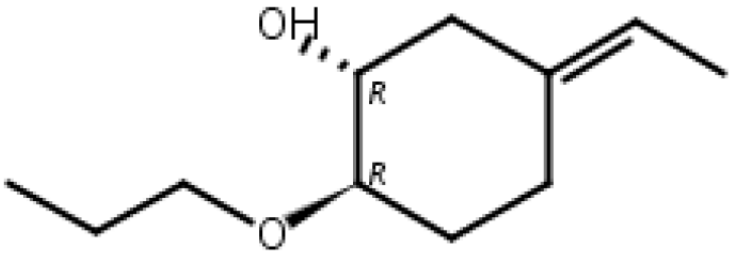
CHEMICAL NAME
STD/1617: Cyclohexanol, 4-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-
STD/1618: Cyclohexanol, 5-ethylidene-2-propoxy-, (1*R*,2*R*)-*rel*-

MOLECULAR FORMULA
$C_{11}H_{20}O_2$

STRUCTURAL FORMULA



Relative stereochemistry., Double bond geometry unknown.
STD/1617



Relative stereochemistry., Double bond geometry unknown.

STD/1618

MOLECULAR WEIGHT
184.28 Da

ANALYTICAL DATA
Reference NMR, IR, GC, GC-MS, UV/Visible spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 90% (isomer mixture)
The notified chemicals (two isomers) are manufactured as part of the same reaction mixture.
STD/1617: present at approximately 40% of the reaction mixture
STD/1618: present at approximately 50% of the reaction mixture

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name	4-ethyl-6-propoxycyclohex-3-en-1-ol		
CAS No.	Not assigned	*Weight %*	0-5
Chemical Name	3-ethyl-6-propoxycyclohex-3-en-1-ol		
CAS No.	Not assigned	*Weight %*	0-5

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES
The following physico-chemical properties are for the reaction mixture containing the two notified chemicals.

APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	249 °C at 102.8 kPa	Measured
Density	961 kg/m^3 at 20 °C	Measured
Vapour Pressure	9 × 10^{-3} kPa at 20 °C	Measured
Water Solubility	5.198 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemicals are unlikely to hydrolyse significantly in the environment pH of 4-9.
Partition Coefficient (n-octanol/water)	log Pow = 2.46 at 20-25 °C	Measured. May partition to phase boundaries based on its potential surface activity.
Surface Tension	53 mN/m at 20 °C	Measured. The value is indicative of surface activity.
Adsorption/Desorption	log Koc = 2.07	Measured. Expected to have high mobility in soil.
Dissociation Constant	Not determined	No dissociable functionality

Flash Point	204 °C at 100.7 kPa	Measured
Flammability limits	Not tested	-
Autoignition Temperature	272 °C at 101.4-101.5 kPa	Measured
Explosive Properties	Not expected to have explosive properties	Estimated based on chemical structure
Oxidising Properties	Not expected to have oxidising properties	Estimated based on chemical structure

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties of the reaction mixture containing the two notified chemicals, refer to Appendix A.

Reactivity
The notified chemicals are 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 chemicals are not recommended for hazard classification according to the *Globally Harmonised System of 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 chemicals are constituents of a reaction mixture, which will be imported as components of finished fragrance oils. The fragrance oils will contain the isomer mixture at 1-10% concentration.

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

STD/1617

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

STD/1618

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

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
International Flavours and Fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemicals will be imported as constituents of finished fragrance oils in 208 L polypropylene-lined steel drums. The imported products containing the notified chemicals will be transported to reformulation sites within Australia by road. The end-use products will be packaged in containers suitable for retail sale.

USE
The notified chemicals will be used as fragrance ingredients. The notified chemicals will be imported as a component of finished fragrance oils (at ≤ 10% concentration) and incorporated into a variety of cosmetic and household products in Australia.

The proposed use concentrations of the isomer mixture containing the notified chemicals in finished consumer products are shown below:

Product Type	*Maximum Combined Use Concentration (%)*
Body lotion	2
Face cream	2
Hand cream	2

Product Type	*Maximum Combined Use Concentration (%)*
Deodorant	1
Fine fragrances	3
Other leave on cosmetics (such as hair spray, hair styling products, makeup remover)	1
Wash off personal care (such as shampoo, shower gel, hand wash soap, facial cleanser)	1
Household, home care (candles, air freshener) and other consumer products	1

OPERATION DESCRIPTION

The notified chemicals will not be manufactured within Australia. No reformulation or repackaging of the notified chemicals will occur at the notifier's facility. The imported fragrance oils containing the notified chemicals (at ≤ 10% concentration for the isomer mixture) will be stored at the notifier's facility until they are sold and distributed to customer facilities for reformulation into end-use products (cosmetic and household products).

Reformulation

The procedures for incorporating the notified chemicals into end-use products will likely vary depending on the nature of the formulated products and may involve both automated and manual transfer steps. However, in general, it is expected that for the reformulation process, the notified chemicals will be weighed and added to the mixing tank where they will be blended with additional additives to form the finished cosmetic and household products. This will be followed by automated filling of the reformulated products into containers of various sizes. The blending operations are expected to be highly automated and use closed systems and/or adequate ventilation. During the reformation process, samples of the notified chemicals and the finished end-use products will be taken for quality control testing.

End use

Cosmetic products

The finished cosmetic products containing the notified chemicals at up to 3% will be used by consumers and professionals such as beauticians and hairdressers. Depending on the nature of the products, applications may be by hand, spray or through the use of applicators.

Household products

Household products containing the notified chemicals at up to 1% may be used by consumers and professional workers such as cleaners. The products may be used in either closed systems with episodes of controlled procedures, for instance automatic washing machine cycles, or open manual processes including spraying, brushing, dipping, wiping and rinsing.

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 and warehouse workers	Incidental	Incidental
Plant operators – Compounding	4	250
Plant operators – Drum handling	1	250
Plant operators – Drum cleaning	2	200
Plant operators – Maintenance	2	250
Plant operators – Quality control	1	250

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemicals as components of fragrance oils (at up to 10% concentration for the isomer mixture), only in the unlikely event of accidental rupture of the drum containers.

Reformulation
During reformulation at the consumer product manufacture facilities, dermal, ocular and perhaps inhalation exposure of workers to the notified chemicals (at ≤ 10% concentration for the isomer mixture) may occur during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. The notifier stated in the submission that the exposure is expected to be minimised by the use of engineering controls including local exhaust ventilation and enclosed systems, and by the use of PPE such as coveralls, goggles, impervious gloves and appropriate respiratory protections.

End-use
Exposure to the notified chemicals in end-use products (at ≤ 3% concentration for the isomer mixture) may occur in professions where the services provided involve the application of cosmetic products to clients (i.e., hair and beauty salons) or the use of cleaning products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers to the notified chemicals is expected to be of a similar or lesser extent than that experienced by consumers using the same products.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemicals (at ≤ 3% concentration for the isomer mixture) through the use of a wide range of cosmetic and household products. The main routes of exposure will be dermal, while ocular and inhalation exposure (e.g. through the use of spray products) is also possible.

Data on typical use patterns of various types of consumer products in which the isomer mixture containing the notified chemicals may be used are shown in the following tables (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of exposure assessment via the dermal route, Australian use patterns for various products are assumed to be similar to the consumer use patterns in Europe. In the absence of dermal absorption data and based on the low molecular weight of the notified chemicals (194.31 Da), a dermal absorption (DA) of 100% was assumed (European Commission, 2003). For inhalation exposure estimation of spray products, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009) with an adult inhalation rate of 20 m^3/day (enHealth, 2012). It was conservatively assumed that the fraction of the notified chemicals inhaled will be 50%, with the remainder ending up on the targets as intended. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was applied in the calculations.

Cosmetic products (dermal exposure)

Product type	*Amount (mg/day)*	*Chemical concentration (%)*	*Retention Factor (RF)*	*Daily systemic exposure (mg/kg bw/day)*
Body lotion	7820	2	1.000	2.4438
Face cream	1540	2	1.000	0.4813
Hand cream	2160	2	1.000	0.6750
Fine fragrance	750	3	1.000	0.3516
Deodorant	1500	1	1.000	0.2344
Shampoo	10460	1	0.010	0.0163
Conditioner	3920	1	0.010	0.0061
Shower gel	18670	1	0.010	0.0292
Hand wash soap	20000	1	0.010	0.0313
Hair styling products	4000	1	0.100	0.0625
Total				**4.3313**

Daily systemic exposure = (Amount × Chemical concentration × RF × DA)/BW
(RF = retention factor; DA = dermal absorption; BW = body weight)

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	*Amount (g/use)*	*C (%)*	*Product Retained (%)*	*Product Transferred (%)*	*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 × DA)/BW

(C = chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

Household products (Direct dermal exposure)

Product type	*Frequency (use/day)*	*C (%)*	*Contact Area (cm^2)*	*Product Usage (g/cm^3)*	*Film Thickness (cm)*	*Time Scale Factor*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	1.43	1	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1	1980	1	0.01	0.007	0.0216
Total							**0.0244**

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness × Time Scale Factor × DA/ BW
(C = chemical concentration; DA = dermal absorption; BW = body weight)

Aerosol products (Inhalation exposure)

Product type	*Amount (g/day)*	*C (%)*	*Exposure Duration Zone 1 (min)*	*Exposure Duration Zone 2 (min)*	*Volume Zone 1 (m^3)*	*Volume Zone 2 (m^3)*	*Daily systemic exposure (mg/kg bw/day)*
Hairspray	9.89	1	1	20	1	10	**0.0322**

Daily systemic exposure = [(Amount × C × 20 m^3/day Inhalation Rate × 50% Fraction Inhaled × 0.1) / BW × 1440)] × (Exposure Duration Zone 1/Volume Zone 1 + Exposure Duration Zone 2/Volume Zone 2)
(C = chemical concentration; BW = 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 chemicals. This would result in a combined internal dose of 4.4355 mg/kg bw/day for the isomer mixture. It is acknowledged that inhalation exposure to the notified chemicals 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 (screening level) hair spray inhalation exposure assessment parameters, 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 chemicals from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners and deodorants).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the isomer mixture containing the notified chemicals 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	LC50 > 5.20 mg/L/4 hour; low toxicity
Skin irritation (*in vitro*) Skin Corrosion - Human Skin Model Test (EpiDerm)	non-corrosive
Skin irritation (in vitro) Skin Irritation – Reconstructed Human Epidermis Model Test (EpiSkin)	irritating
Eye irritation (*in vitro*) Bovine Corneal Opacity and Permeability Test	Not corrosive or severely irritating
Rabbit, eye irritation	irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity with reproductive / developmental toxicity screening	Systemic and reproductive / developmental effects: NOAEL = 894 (female) and 870 (male) mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell micronucleus test	non genotoxic

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemicals were submitted.

Given the low molecular weight (184.28 Da) of the notified chemicals and the log Kow of 2.46, absorption across biological membranes may occur.

Acute toxicity
The notified chemicals are of low acute oral, dermal and inhalation toxicity based on studies conducted in rats.

Irritation
The notified chemicals are irritating to the skin based on the results of *in vitro* skin irritation and corrosion studies conducted using a reconstructed human epidermis model. On the basis of these studies, the notified chemicals are considered to skin irritants (Cat 2) according to the GHS criteria.

Based on the results of an eye irritation study in rabbits, the notified chemicals are irritating to the eyes (Category 2A) according to the GHS criteria. An in-vitro eye irritation test was also conducted using the Bovine Corneal Opacity and Permeability (BCOP) test method. The notified chemicals were found to be not corrosive or severely irritating to the eyes in this study.

No information was available on the potential for respiratory irritation of the notified chemicals.

Sensitisation
In a mouse Local Lymph Node Assay, the notified chemicals showed no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation.

Repeated dose toxicity
In a combined repeated dose oral toxicity study with reproductive/developmental toxicity screening, a NOAEL for systemic effects was established as 894 (female) and 870 (male) mg/kg bw/day for the notified chemicals (the highest doses tested, based on the absence of adverse effects at this dose).

As there was no effect of the test substance on male and female fertility, reproductive performance, litter data or pup clinical signs, sex ratios and survival in this study, the NOAEL for fertility and reproduction was also established as 894 (female) and 870 (male) mg/kg bw/day.

Mutagenicity/Genotoxicity
The notified chemicals were not mutagenic in a bacterial reverse mutation assay and were not considered to be genotoxic in an *in vitro* mammalian cell micronucleus test.

Health hazard classification
Based on the available information, the notified chemicals are 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***
Skin Corrosion/Irritation (Category 2)	H315 – Causes skin irritation
Serious Eye Damage/Eye irritation (Category 2A)	H319 – Causes serious eye irritation

6.3. Human Health Risk Characterisation
The notified chemicals are skin and eye irritants. No data are available on respiratory irritation.

6.3.1. Occupational Health and Safety
Reformulation
Transport, storage and reformulation workers may have dermal contact with the notified chemicals at up to 10% concentration. Accidental ocular exposure is also possible. At 10% concentration there is a potential for irritation effects. Safe work practices when handling the notified chemicals during reformulation processes and use of PPE including impervious gloves, coveralls and eye protection would limit exposure and risk.

Provided that the above mentioned control measures and PPE are employed, the risk to the health of workers during the handling of the notified chemicals at up to 10% concentration is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemicals at up to 3% concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemicals is expected to be of a similar or lesser extent than that experience 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 public may experience repeated exposure to the notified chemicals through the use of cosmetic and household products (containing the notified chemicals at ≤ 3% in individual products). The main route of exposure is expected to be dermal with some potential for inhalation and for accidental ocular or oral exposure.

Local effects
The notified chemicals are irritating to the skin and eyes. However, given the relatively low proposed use concentration (≤ 3%), significant irritation effects are not expected.

Systemic effects
The potential systemic exposure to the public from the use of the notified chemicals in cosmetics and household products was estimated to be 4.4355 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 870 mg/kg bw/day, which was derived from an oral combined repeated dose toxicity study with a reproductive/developmental toxicity screening test in male rats, the margin of exposure (MOE) was estimated to be 196. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemicals at ≤ 3% in fine fragrances, ≤ 2% in other cosmetics and ≤ 1% in household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemicals will be imported as a component of finished fragrance oils for reformulation into cosmetic and household products. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemicals are expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

The fragrance formulations containing the notified chemicals will be blended with other ingredients within a fully enclosed environment, in the manufacture of cosmetic and household products. The process is expected to be followed by automated filling of the formulated products into containers of various sizes suitable for retail sale and end-use. Wastes containing the notified chemicals generated during reformulation include equipment wash water, empty import containers and spilt materials. Empty import containers and wash waters are expected to be recycled during subsequent blending processes or released to sewers, or disposed of to landfill in accordance with local government regulations. In the event of a spill, the notified chemicals are expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

RELEASE OF CHEMICAL FROM USE
The notified chemicals are expected to be released to the aquatic compartment through sewers during their use in various cosmetic formulations and household products across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL
It is expected that some of the product containing the notified chemicals will remain in end-use containers. Wastes and residue of the notified chemicals 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 Australia, the majority of the notified chemicals are expected to be released to sewers on a nationwide basis. The notified chemicals are not readily biodegradable (6% in 28 days). For the details of the environmental fate studies, please refer to Appendix C.

The half-life of the notified chemicals in air is calculated to be 0.99 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA 2011). Therefore, in the event of release to atmosphere, the notified chemicals are not expected to persist in the atmospheric compartment.

A significant proportion of the notified chemicals may remain in the aqueous phase in the sewage treatment plants (STPs) and be released to surface waters based on their high water solubility, medium partition and adsorption coefficients and lack of ready biodegradability. A proportion of the notified chemicals may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. The notified chemical residues in landfill and soils are expected to have high mobility based on their soil adsorption coefficient (log Koc = 2.07). However, the notified chemicals have low potential to bioaccumulate based on their octanol-water partition coefficient value (log P_{OW} = 2.46) and potential surface activity. In surface waters, soils and landfill, the notified chemicals are expected to eventually degrade through both biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleaning products, it is assumed that 100% of the total import volume of the notified chemicals is released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that there is no removal of the notified chemicals during sewage treatment processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	10,000*	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	27.40	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	5.62	µg/L
PEC - Ocean:	0.56	µg/L

*Based on the combined import volume of STD 1617 and 1618

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 chemicals in this volume are 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 5.62 µg/L may potentially result in a soil concentration of approximately 37.45 µg/kg. Assuming accumulation of the notified chemicals in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemicals in the applied soil in 5 and 10 years may be approximately 187.3 µg/kg and 374.5 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemicals 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 = 125 mg/L	Not harmful to fish
Daphnia Toxicity	48 h EC50 >100 mg/L	Not harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 > 100 mg/L NOEC = 1 mg/L	Not harmful to algae

Based on the above acute ecotoxicological endpoints, the notified chemicals are not expected to be harmful to aquatic organisms on acute basis. Therefore, the notified chemicals are not formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* (United Nations, 2009) for acute toxicities. Based on their lack of ready biodegradability and NOEC value for algae, the notified chemicals are formally classified as "Chronic Category 2; Toxic to aquatic life with long lasting effects" under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive chronic endpoint (NOEC) for algae and assessment factor of 100 given three acute endpoints for three trophic levels and one chronic endpoint are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Alga).	1.00	mg/L
Assessment Factor	100.00	
Mitigation Factor	1.00	
PNEC:	10.00	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	5.62	10	0.562
Q - Ocean:	0.56	10	0.056

The Risk Quotients (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemicals have been calculated to be < 1 for both river and ocean compartments indicating that the notified chemicals are unlikely to reach ecotoxicologically significant concentrations in surface waters based on the maximum annual importation quantity. The notified chemicals are not expected to bioaccumulate. On the basis of the PEC/PNEC ratio and assessed use pattern, the notified chemicals are not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -20 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	No freezing or restriction of surface movement was noted at temperatures down to -24.7 °C.
Test Facility	Chilworth (2015)

Boiling Point 249 °C at 102.8 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Differential scanning calorimetry method was used.
Test Facility	Envigo (2016 a)

Density 961 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 pycnometer method was used.
Test Facility	Envigo (2016a)

Vapour Pressure 9×10^{-3} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Static method was used.
Test Facility	Chilworth (2015)

Water Solubility 5.198 g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	Chilworth (2015)

Partition Coefficient (n-octanol/water) log Pow = 2.46 at 20-25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Flask Method
Test Facility	Chilworth (2015)

Surface Tension 53 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	Concentration: 1.0 g/L.
Test Facility	Envigo (2016a)

Adsorption/Desorption log K_{oc} = 2.07

Method	OECD TG 121 estimation of the adsorption coefficient (K_{oc}) on soil and on sewage sludge using high performance liquid chromatography (HPLC).
Remarks	A cyanopropyl reverse phase HPLC column containing lipophilic and polar moieties was utilised.

Test Facility Envigo (2016b)

Flash Point 204 ± 2 °C at 100.7 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point
Remarks A closed cup flash point tester was used.
Test Facility Envigo (2016c)

Autoignition Temperature 272 ± 5 °C at 101.4-101.5 kPa

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks A carbolite flask heater was used.
Test Facility Envigo (2016c)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks The prediction was based on the chemical structure.
Test Facility Envigo (2016c)

Oxidizing Properties Predicted negative

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks The prediction was based on the chemical structure.
Test Facility Envigo (2016c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: The isomer mixture containing the notified chemicals

METHOD: OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001)
EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class 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	3 F	300	0/3
2	3 F	2,000	0/3
3	3 F	2,000	0/3

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Hunched posture and ataxia were observed in animals of group 2 treated at a dose level of 2,000 mg/kg. Other signs of systemic toxicity noted in one of these animals were decreased respiratory rate, prostration and increased salivation. All animals in this group appeared normal on the first day after dosing. No signs of systemic toxicity were observed in other two groups.
Effects in Organs	No abnormities were observed at necropsy.
Remarks - Results	All animals had expected body weight gain during the observation period.

CONCLUSION: The test substance is of low toxicity via the oral route.

TEST FACILITY: Envigo (2016d)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: The isomer mixture containing the notified chemicals

METHOD: OECD TG 402 Acute Dermal Toxicity – Limit Test (1987)
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	No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No signs of dermal irritation were noted.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed.
Effects in Organs	No abnormities were observed at necropsy.
Remarks - Results	All animals had expected body weight gain during the observation period.

CONCLUSION: The test substance is of low toxicity via the dermal route.

TEST FACILITY: Envigo (2016e)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009)
Species/Strain	Rat/Wistar
Vehicle	None
Method of Exposure	Oro-nasal
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	Mass median aerodynamic diameter = 3.83 ± 0.13 μm with an average geometric standard deviation of 1.86 ± 0.05
Remarks - Method	No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	19.3	5.20 ± 0.03	0/10

LC50	> 5.20 mg/L/4 hours
Signs of Toxicity	No mortality was seen. During exposure, all animals exhibited breathing abnormalities characterised by a decreased breathing rate and shallow breathing. The severity of these findings increased during the course of the exposure period, and males (showing slight to moderate abnormalities firstly noted shortly after initiation of exposure) were more severely affected than females (showing slight abnormalities during the second half of the exposure period). Breathing abnormalities and general signs of discomfort were less severe at the end of the day of dosing. During the 14-day post-exposure observation period, some transient clinical signs were observed, which resolved in one to three days. In addition, cataract was noted in one male from day seven until the day of sacrifice, and vocalisation was observed in one female from day one to twelve.
Effects in Organs	At scheduled necropsy at the end of the 14-day observation period there were red spots on one or more lung lobes of one female and four male animals indicating pulmonary haemorrhages. No macroscopic lesions were found in the five remaining animals.
Remarks - Results	A slight loss of body weight was noted in most animals on the day after exposure (on average 5% in males and 1% in females). All animals recovered from the initial body weight loss within a week and exhibited normal growth during the second week of the observation period.
CONCLUSION	The test substance is of low acute toxicity via inhalation.
TEST FACILITY	Triskelion (2016a)

B.4. Irritation – skin (*in vitro*)

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
METHOD	OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test (2015) EC Council Regulation No 440/2008 B.40 BIS. *In vitro* Skin Corrosion - Human Skin Model Test
Vehicle	None
Remarks - Method	The EpiDerm test system was used. No protocol deviations were noted. The positive control used was 8N potassium hydroxide and the negative control was sterile distilled water.

RESULTS

Exposure of 3 minutes

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*
Negative control	1.729 ± 0.042	100*
Test substance	1.799 ± 0.060	104.0
Positive control	0.081 ± 0.006	4.7

Exposure of 60 minutes

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*
Negative control	1.947 ± 0.144	100*
Test substance	1.500 ± 0.086	77.0
Positive control	0.086 ± 0.006	4.4

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

Remarks - Results: Results for the test substance were similar to the results of the negative control at both exposure durations.

The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) solution containing the test substance did not turn blue, confirming that the test substance did not reduce MTT. The solution containing the test substance did not become coloured, indicating that the test substance did not have the potential to cause colour interference.

The acceptance criteria for both the negative and positive controls were satisfied, and the variation between replicates was satisfactory.

As the relative mean viability of tissues exposed to the test substance was > 50% after both 3 minutes and 60 minutes exposure, the test substance did not meet the criteria for classification as a Cat.1 corrosive under the GHS.

CONCLUSION: The test substance was non-corrosive to the skin under the conditions of the test.

TEST FACILITY: Envigo (2016f)

B.5. Irritation – skin (*in vitro*)

TEST SUBSTANCE: The isomer mixture containing the notified chemicals

METHOD: OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method (2015)
EC Council Regulation No 440/2008 B.46. *In vitro* Skin Irritation – Reconstructed Human Epidermis Model Test (2015)

Vehicle: None

Remarks - Method: The EpiSkin test system was used. The positive control was 5% sodium dodecyl sulfate (SDS) and the negative control was phosphate buffered saline (PBS). A protocol deviation in which tissues were pre-incubated for 2 h rather than overnight was considered not to affect the validity of the study.

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*
Negative control	1.177 ± 0.026	100*
Test substance	0.049 ± 0.008	4.1
Positive control	0.049 ± 0.012	4.2

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

Remarks - Results	The test substance showed reduced cell viability, similar to the results of the positive control. The solution containing the test substance was colourless and therefore it was unnecessary to run colour correction tissues. The MTT solution containing the test substance did not turn blue, indicating that the test substance did not reduce MTT. The criteria for acceptance of both the negative and positive controls were satisfied, as were the requirements for standard deviation between the replicates. The test substance meets the criteria for classification as a Cat. 2 skin irritant under the GHS as the relative mean viability of the tissues treated with the test substance in this study was < 50%.
CONCLUSION	The test substance was irritating to the skin under the conditions of the test.
TEST FACILITY	Envigo (2016g)

B.6. Irritation – eye (*in vitro*)

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
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 (2013)
Vehicle	None
Remarks - Method	The positive control was ethanol and the negative control was 0.9% sodium chloride solution. No protocol deviations were reported.

RESULTS

Test material	*Opacity*	*Mean opacities of triplicate tissues*	*IVIS*
Vehicle control	0.3	0.035	0.9
*Test substance**	10.7	0.522	18.5
*Positive control**	26.7	1.366	47.2

IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results	Both post treatment and post incubation, the corneas treated with the test substance were slightly cloudy, the corneas treated with the negative control were clear, and the corneas treated with the positive control were cloudy. The criteria for acceptance of both the negative and positive were satisfied, and the three results for the test substance did not show high variability..
CONCLUSION	The test substance did not meet the criteria for classification as category 1 eye irritant or not requiring classification for eye irritation or serious eye damage.
TEST FACILITY	Envigo (2016h)

B.7. Irritation – eye

TEST SUBSTANCE	The isomer mixture containing the notified chemicals

METHOD OECD TG 405 Acute Eye Irritation/Corrosion (2012)
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	1 M, 1 F
Observation Period	14 days
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			
Conjunctiva: redness	2	2	2	< 14 d	0
Conjunctiva: chemosis	1.7	2	3	< 7 d	0
Conjunctiva: discharge	1.3	1.7	2	< 14 d	0
Corneal opacity	1	1	1	< 7 d	0
Iridial inflammation	0.3	1	1	< 7 d	0

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

Remarks - Results

Diffuse corneal opacity was noted in both treated eyes at the 24, 48 and 72-hour observations.

Iridial inflammation was observed in both treated eyes 1 and 24 hours after treatment and persisted in the treated eye of one animal at the 48 and 72-hour observations.

Moderate conjunctival irritation was noted in both treated eyes 1 hour after treatment and at the 24, 48 and 72-hour observations. Minimal conjunctival irritation was observed in the treated eye of one animal at the 7-day observation.

All ocular effects had resolved in one animal at the 7-day observation and in the remaining animal at the 14-day observation.

The female animal had gained weight (measured at 7 days) and the male animal lost weight slightly (measured at 14 days).

CONCLUSION The test substance is irritating to the eye.

TEST FACILITY Envigo (2016i)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE The isomer mixture containing the notified chemicals

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010)
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil 4:1
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde
Remarks - Method	No protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (SI) (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	981.53 ± 325.31	-
25	5 F	1479.90 ± 489.80	1.51
50	5 F	952.97 ± 581.96	0.97
100	5 F	2121.22 ± 1084.64	2.16
Positive Control			
25	5 F	8480.35 ± 4605.71	8.64

Remarks - Results: There were no deaths. No signs of systemic toxicity were observed in the test or control animals. Body weight change of test animals between day 1 and 6 was comparable to that noted in the corresponding control animals over the same period.

SI < 3 at all tested concentrations

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.

TEST FACILITY: Envigo (2016j)

B.9. Repeat dose toxicity, with reproductive/developmental toxicity screening

TEST SUBSTANCE: The isomer mixture containing the notified chemicals

METHOD: OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (1996)

Species/Strain: Rat/Wistar

Route of Administration: Oral – diet

Exposure Information: Total exposure days:
male: a premating period of 2 weeks and during mating;
female: a premating period of 2 weeks and during mating, gestation until day 4 of lactation.
Dose regimen: 7 days per week (ad libitum)
Post-exposure observation period:

Vehicle: VRF1 (FG) diet

Remarks - Method: Minor deviation did not affect the validity of the study.

The dose levels were selected on the basis of a 14-day range finding study in which groups of 4 male and 4 female rats were fed 0, 300, 1,500, 7,500 and 15,000 mg/kg bw/day diet.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (mg/kg diet/day)	*Actual (mg/kg bw/day)*	
control	12 per sex	0	0	1 M
low dose	12 per sex	1,500	104 (F) 85 (M)	0/24
mid dose	12 per sex	5,000	333 (F) 280 (M)	0/24
high dose	12 per sex	15,000	894 (F) 870 (M)	0/24

Mortality and Time to Death

One control male died during the mating period (day 4). The death of this rat was not treatment-related.

Clinical Observations

There were no treatment-related clinical signs or statistically significant or treatment-related differences in body weights during the premating period, the post-mating period, the gestation period or the lactation period.

Clinical observations outside the home cage, functional observation battery and motor activity assessment did not show any neurotoxic potential.

There were no marked differences in food consumption between the test groups and the controls. Mean food intake in the high dose group females was statistically significantly lower in the first week of the premating period, but recovered. This was considered to be related to the palatability of the test substance. In the post-mating period (for males) and during gestation and lactation no difference in food consumption was observed as compared to the controls.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

For haematology, there were no treatment related or statistically significant changes in red blood cell or clotting variables or white cell parameters.

For clinical chemistry, phospholipids were statistically significantly increased in both males and females of the high dose group and glucose plasma levels were statistically significantly decreased in females of the high dose group. These effects were considered by the study authors to be related to treatment, but not adverse in the absence of histopathological changes.

In the absence of a dose response relationship, statistically significant differences in PO_4 in males of the low dose and mid dose group were not considered to be related to treatment.

Aspartate aminotransferase activity (ASAT) and alanine aminotransferase activity (ALAT) activity were statistically significantly decreased in males (ASAT in the low dose group and both in the high dose group). However, ALAT activity was within the historical control range. For ASAT and ALAT activity, an increase rather than a decrease is considered to represent a toxic effect. Therefore, these findings were not considered toxicologically relevant.

Effects in Parental Organs

Mean liver weight and kidney weight increases in the males of the high dose group were statistically significant. In females of the high dose group a trend towards increased mean liver weight and kidney weight was not statistically significant. There were no statistically significant weight changes in the other organs.

Macroscopic or microscopic observations at necropsy revealed no treatment related abnormalities.

Fertility was not affected by the treatment. The male and female mating index was 100 % in all groups. All females were mated except one female in the control group. There were no treatment related differences in pre-coital time.

Reproductive performance was not affected by the treatment. All mated females were pregnant and had live litters. In each group the duration of gestation was comparable and the gestation index was 100%.

No differences were found on the mean number of corpora lutea and implantation sites between the groups and pre-implantation loss was not impacted by the treatment.

No treatment related differences were observed in prenatal or perinatal loss. No litters were with stillborn pups. One pup in the control group was dead. One pup in the mid dose group and two pups in the high dose group were cannibalised.

Litter Data

The number of pups delivered and the sex ratio of the pups were comparable in the various groups. Live birth index was 100% in all groups. The viability index (four-day survival) was not affected by the treatment.

One pup in the control group and one pup in the high dose group showed a wound. Another pup in the control group showed cyanosis. There were no treatment related signs in pups during the lactation period.

No relevant or statistically significant differences were noted in mean pup weight between the test groups and the controls on day 0 or day 4 of lactation.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 894 (female) and 870 (male) mg/kg bw/day in this study, based on the absence of adverse effects at the highest dose tested. A No Observed Effect Level (NOEL) was established as 333 (female) and 280 (male) mg/kg bw/day in this study, based on the absence of treatment related effects at these dose levels.

As there were no test substance related effects on male and female fertility, reproductive performance, litter data or pup signs, sex and survival, the NOAEL for fertility and reproduction was established as 894 (female) and 870 (male) mg/kg bw/day in this study.

TEST FACILITY Triskelion (2016b)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE The isomer mixture containing the notified chemicals

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997)
Plate incorporation procedure

Species/Strain	*Salmonella typhimurium strains*: TA1535, TA1537, TA98, TA100 *Escherichia coli strains*: WP2uvrA
Metabolic Activation System	Aroclor-induced rat liver S9
Concentration Range in Main Test	a) With metabolic activation: 0, 1.5, 5.0, 15, 50, 150, 500, 1,500 and 5,000 µg/plate b) Without metabolic activation: 0, 1.5, 5.0, 15, 50, 150, 500, 1,500 and 5,000 µg/plate
Vehicle	DMSO
Remarks - Method	No protocol deviations. The criteria for an increase in revertants considered to be positive was two fold for TA 98, TA 100, and WP2uvrA, and three fold for TA 1535 and TA 1537. The preliminary test is reported as test 1.

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	≥ 1,500	> 5,000	negative
Present			
Test 1	≥ 5,000	> 5,000	negative
Test 2	≥ 5,000	> 5,000	negative

Remarks - Results No positive mutagenicity responses or dose-related increases in revertants were noted with any of tester strains in either the presence or absence of S9 activation. There was a non-dose related increase in revertants in Test 1 for TA 1537 in the absence of metabolic activation. However it did not reach a threefold increase. Neither precipitate nor background lawn toxicity was observed. However, reductions in revertant counts were observed from 1,500 or 5,000 µg per plate with several test strains.

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

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

TEST FACILITY BioReliance Corporation (2015a)

B.11. Genotoxicity – *in vitro*

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
METHOD	OECD TG 487 *In vitro* Mammalian Cell Micronucleus Test (2010)
Cell Type/Cell Line	Human peripheral blood lymphocytes
Metabolic Activation System	Aroclor-induced rat liver S9
Vehicle	DMSO
Remarks - Method	Doses were chosen on the basis of a preliminary toxicity test. No protocol deviations. The positive controls used are cyclophosphamide, mitomycin C and vinblastine.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 50, 150, 300, 600, 800*, 1,000*, 1,200*, 1,400, 1,600, 1,800	4 h	24 h
Test 2	0*, 50*, 150, 200*, 250, 300*, 350, 400, 450, 500, 550	24 h	24 h
Present			
Test 1	0*, 50, 150, 300*, 600*, 800, 1,000*, 1,200, 1,400, 1,600, 1,800	4 h	24 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	1,840			
Test 1		≥ 1,200	≥ 1,600	negative
Test 2		≥ 300	> 550	negative
Present	≥ 552			
Test 1		≥ 1,000	≥ 1,800	negative

Remarks - Results

At the highest concentration in each test group, cytoxicity ranged from 50-58%.

No statistically significant increase in the percentage of cells with micronucleated binucleated cells was seen in Test 2 without metabolic activation, or in Test 1 with metabolic activation.

In Test 1 without metabolic activation (4-hour exposure group) there was a statistically significantly increase relative to vehicle control at 800 μg/mL ($p \leq 0.05$). However, this was not dose related and the percentage of micronucleated binucleated cells in the test article-treated group (0.4%) was within the historical solvent control range of 0.1% to 1.6%. Therefore, the statistically significant increase was not considered by study authors to be biologically relevant.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the validity of the test.

CONCLUSION	The test substance was not clastogenic to human peripheral blood lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	BioReliance Corporation (2015b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Carbon Dioxide ($ThCO_2$)
Remarks - Method	The following deviation from the test protocol was reported. On Days 25 and 26 of the study the temperature in a vessel containing water which was incubated under the same conditions as the test vessels was recorded as being 24.8 °C. This was a deviation from the test protocol which states the test will be conducted at a temperature of 22 ± 2 ºC. This deviation was not considered to have affected the integrity or validity of the study given that all validation criteria were met.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	1	6	51
8	1	8	65
10	1	10	66
14	6	14	85
21	5	21	84
29*	6	29*	107

* Corrected for the last gas wash

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate, surpassed the threshold level of 60% by 14 days (85%), therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 6 days (31%; 37% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The test item attained 6% biodegradation after 28 days and, therefore, cannot be considered to be readily biodegradable under the terms of OECD Guideline No. 301B.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	Envigo (2016k)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
METHOD	OECD TG 203 Fish, Acute Toxicity Test –Semi-static
Species	*Danio rerio* (zebrafish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	60 mg $CaCO_3$/L

Analytical Monitoring	GC-MS
Remarks – Method	No significant deviations to the test protocol were reported.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
80	75	7	0	0	0	0	0
89.6	81	7	0	0	0	0	0
100.4	97	7	0	0	0	0	0
112.4	108	7	0	0	14.3	14.3	14.3
125.9	123	7	0	14.3	57.1	57.1	57.1
141	137	7	0	85.7	85.7	85.7	85.7

LC50	125 mg/L (95% CI 117-136 mg/L) at 96 hours
NOEC (or LOEC)	Not determined
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 48 hours during the 96 h test period. The actual concentrations of the test substance were measured before and after renewal and at the start and end of the test period. The measured actual concentrations were within ± 20% difference of the nominal concentrations. Therefore, the 96 h LC_{50} for fish was determined to be 125 mg/L, based on nominal concentrations.

CONCLUSION	The test substance is not considered to be harmful to fish.
TEST FACILITY	Suzhou Xishan Zhongke Drug R&D Co., Ltd. (2015)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	The isomer mixture containing the notified chemicals
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	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 [acute]*	*48 h [acute]*
Control	<limit of quantification>	20	0	0
10		20	0	0
18		20	0	0
32		20	0	5
56	55.5	20	0	5
100	92.7	20	10	40

EC50	>100 mg/L at 48 hours
NOEC	56 mg/L at 48 hours
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 nominal 0, 56 and 100 mg/L test substance preparations were measured at the start and end of the 48 h test period. Since the mean of these measured notified chemical test medium

concentrations remained within ± 20 % of the nominal concentrations, the effect values were based on the nominal concentrations of the notified chemical. The 48 h EC_{50} for *D. magna* was >100 mg/L, based on nominal concentrations of the notified chemical.

CONCLUSION The test substance is not considered to be harmful to aquatic invertebrates.

TEST FACILITY Envigo (20161)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE The isomer mixture containing the notified chemicals

METHOD OECD TG 201 Alga, Growth Inhibition Test - Static

Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1 - 100 mg/L Actual: 0.86 – 96.3 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
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*	
EyC50 *mg/L at 72 h*	*NOEC / LOEC* *mg/L*	*ErC50* *mg/L at 72 h*	*NOEC / LOEC* *mg/L*
32	1.0 / 3.2	> 100	1.0 / 3.2

Remarks - Results All 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 start and end of the 72 h test period. As the mean measured concentrations were near nominal concentrations all effects values were calculated based on nominal concentrations. The notified chemicals had ErC_{50} >100 mg/L and NOEC 1.0 mg/L.

CONCLUSION The test substance is not considered to be harmful to algae.

TEST FACILITY Envigo (2016m)

BIBLIOGRAPHY

ACI (2010) Consumer Product Ingredient Safety, Exposure and Risk Screening methods for Consumer Product Ingredients, 2nd Edition, American Cleaning Institute, Washington DC.

BioReliance Corporation (2015a) Bacterial Reverse Mutation Assay (BioReliance Study Number: AE09SU.503.BTL, February, 2015). USA, BioReliance Corporation, Rockville, MD 20850 (Unpublished report submitted by the notifier).

BioReliance Corporation (2015b) *In Vitro* Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL) (BioReliance Study Number: AE09SU.348.BTL, May, 2015). USA, BioReliance Corporation, Rockville, MD 20850 (Unpublished report submitted by the notifier).

Cadby *et al.* (2002) Cadby, P.A., Troy, W.R., Vey, M.G.; Consumer exposure to fragrance: Providing estimates for safety evaluation, Regulatory Toxicology and Pharmacology 36 (2002) 246-252.

Chilworth (2015) Phys/chem Testing (CTL Study Plan Number: GLP/113246, July, 2015). UK, Chilworth Technology Limited Southampton SO16 7NS (Unpublished report submitted by the notifier).

Earnest, C.W., Jr. (2009) A Two-Zone Model to Predict Inhalation Exposure to Toxic Chemicals in Cleaning Products, MSCEng thesis, The University of Texas at Austin

ECHA (2014) Guidance on information requirements and chemical safety assessment, Chapter R.7c: Endpoint specific guidance, p 172, 2014.

Envigo (2016a) Determination of Boiling Point, Density and Surface Tension (Envigo Study Number: NT33LM, June, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016b) Determination of Adsorption Coefficient (Study Number PC43QK, June, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016c) Determination of Hazardous Phyico-Chemical Properties (Envigo Study Number: PB67XC, August, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016d) Acute Oral Toxicity in the Rat - Acute Toxic Class Method (Envigo Study Number: MF08RK, October, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016e) Acute Dermal Toxicity (Limit Test) in the Rat (Envigo Study Number: SY38PC, October, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016f) *In vitro* EPIDERM™Skin Corrosion Test (Envigo Study Number: MK80GY, July, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016g) Determination of Skin Irritation Potential using the EPISKIN™ Reconstructured Human Epidermis Model (Envigo Study Number: ML31BV, July, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016h) The Bovine Corneal Opacity and Permeability (BCOP) Assay (Envigo Study Number: CF91CK, August, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016i) Acute Eye Irritation in the Rabbit (Envigo Study Number: SG48FB, October, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016j) Local Lymph Node Assay in the Mouse – Individual Method (Envigo Study Number: WQ35LY, October, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016k) Assessment of Ready Biodegradability; CO_2 Evolution Test (Study Number JB39VC, July, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016l) Daphnia sp., 48-Hour Acute Immobilization Test (Study Number BN96BV, June, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

Envigo (2016m) Algal Growth Inhibition Test (Study Number YJ60LX, September, 2016). UK, Envigo Research Limited, Derbyshire DE72 2GD (Unpublished report submitted by the notifier).

enHealth (2012) Australian Exposure Factor Guide, companion document to: Environmental Health Risk Assessment: Guidelines for assessing human health risks from environmental hazards, EnHealth, Commonwealth of Australia.

Loretz *et al.* (2006) Loretz, L., Api, A.M., Barraj, L., Burdick, J., Davis, D.A., Dressler, W., Gilberti, E., Jarrett, G., Mann, S., Pan, Y.H.L., Re, T., Renskers, K., Scrafford, C., Vater, S.; Exposure data for personal care products: Hairspray, perfume, liquid foundation, shampoo, body wash and solid antiperspirant, Food and Chemical Toxicology 44 (2006) 2008-2018.

Rothe *et al.* (2011) Rothe, H., Fautz, R., Gerber, E., Neumann, L., Rettinger, K., Schuh, W., Gronewold, C.; Special aspects of cosmetic spray evaluations: Principles on inhalation risk assessment, Toxicology Letters 205 (2011) 97-104.

Steiling *et al.* (2014) Steiling, W., Bascompta, M., Carthew, P., Catalano, G., Corea, N., D'Haese, A., Jackson, P., Kromidas, L., Meurice, P., Rothe, H., Singal, M..; Principle considerations for the risk assessment of sprayed consumer products, Toxicology Letters 227 (2014) 41-49.

Suzhou Xishan Zhongke Drug R&D Co., Ltd. (2015) Fish, Acute Toxicity Test for FRET 13-0156 (Study No. 2015-154-01-01, December, 2015). Suzhou City, Jiangsu Province, China, Suzhou Xishan Zhongke Drug R&D Co., Ltd.

SWA (2012) Code of Practice: Managing Risks of Hazardous Chemicals in the Workplace, Safe Work Australia, https://www.safeworkaustralia.gov.au/doc/model-code-practice-managing-risks-hazardous-chemicals-workplace

Triskelion (2016a) Acute (4-hour) Inhalation Toxicity Study in Rats (Triskelion Project Number: P10137 (formerly 093.25916), December, 2016). The Netherlands Triskelion B.V. Utrechtseweg 48 (Unpublished report submitted by the notifier).

Triskelion (2016b) Combined Oral Repeated Dose Toxicity Study and Reproduction/Developmental Toxicity Screening Test in Rats (Triskelion Project Number: 093.25508/04, June, 2016). The Netherlands Triskelion B.V. Utrechtseweg 48 (Unpublished report submitted by the notifier).

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

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