File No: LTD/2002

December 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

3-Cyclohexene-1-methanol, α-ethyl-2,4-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

TABLE OF CONTENTS

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2002	International Flavours & Fragrances (Australia) Pty Ltd	3-Cyclohexene-1-methanol, α-ethyl-2,4-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 Solid	H228 – Flammable Solid
Specific target organ toxicity, single exposure (Category 2)	H371 – May cause damage to organs
Serious Eye Damage/Eye irritation (Category 2)	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*
Acute Category 2	H401 - Toxic to aquatic life
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 chemical is not considered to pose an unreasonable risk to the health of workers.

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

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Flammable Solid: H228 – Flammable Solid
  - Specific target organ toxicity, single exposure (Category 2): H371 – May cause damage to organs
  - Serious Eye Damage/Eye irritation (Category 2): 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.

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 processes:
  - Enclosed, automated processes, where possible
  - Local exhaust ventilation and/or appropriate extraction systems where 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 chemical during reformulation processes:
  - Avoid contact with eyes
  - Avoid dust/aerosol inhalation

- 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 processes:
  - Coveralls, impervious gloves, goggles
  - Respiratory protection (if aerosols of the notified chemical are likely to be present)

  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 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.

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 intended to exceed 1% in cosmetic, personal care and household products, with the exception of fine fragrances at 3%, hair spray at 2%, and deodorants at 0.5%.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
International Flavours & Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

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

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: dissociation constant, explosive properties and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
No

NOTIFICATION IN OTHER COUNTRIES
US EPA (2017), China (2017), Japan (2017)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
FRET 11-0571

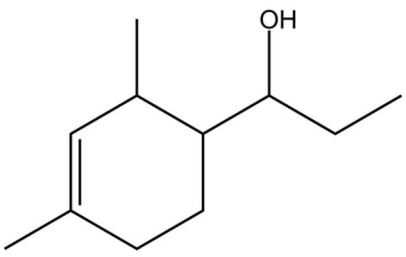
CAS NUMBER
1632042-40-0

CHEMICAL NAME
3-Cyclohexene-1-methanol, α-ethyl-2,4-dimethyl-

OTHER NAME(S)
2,4-Dimethylcyclohex-3-en-1-yl]propan-1-ol (IUPAC name)
FRET 11-0571

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

STRUCTURAL FORMULA



MOLECULAR WEIGHT
168.28 g/mol

3. COMPOSITION

DEGREE OF PURITY
> 95%

The notified chemical is composed of four relative diastereoisomers in the following ratios:
rel-(1R)-1-[(1R,2R)-2,4-dimethylcyclohex-3-en-1-yl]propan-1-ol 15.19%;
rel-(1R)-1-[(1S,2S)-2,4-dimethylcyclohex-3-en-1-yl]propan-1-ol 7.52%;
rel-(1R)-1-[(1S,2R)-2,4-dimethylcyclohex-3-en-1-yl]propan-1-ol 60.81%;
rel-(1R)-1-[(1R,2S)-2,4-dimethylcyclohex-3-en-1-yl]propan-1-ol 13.39%.

HAZARDOUS IMPURITIES
None

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

Chemical Name 3-Cyclohexene-1-methanol, 2,4-dimethyl-
CAS No. 67634-17-7 *Weight %* 1.34

ADDITIVES/ADJUVANTS

Chemical Name Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester
CAS No. 6386-38-5 *Weight %* 0.1

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: White solid

Property	Value	Data Source/Justification
Melting Point	23-60 °C	Measured
Boiling Point	231.9 °C at 102kPa	Measured
Density	958 kg/m^3 at 20 °C	Measured
Vapour Pressure	16.84 Pa at 20 °C	Measured
Water Solubility	496 mg/L at 20 °C	Measured
Hydrolysis as a Function of pH	Hydrolytically stable at pH 4,7, and 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.68 at 20-25 °C	Measured. May partition to phase boundaries based on potential surface activity.
Adsorption/Desorption	log K_{oc} = 1.83 and 2.36 at 25 °C	Measured
Surface Tension	48.5 mN/m at 20 °C	Measured. The measured value is indicative of potential surface activity
Dissociation Constant	Not determined	The notified chemical does not contain functionality that is expected to dissociate under environmental conditions
Particle Size	Not determined	The notified chemical is a paste-like solid; in addition it will only be introduced into Australia in solution form and will not be separated from the solution.
Flash Point	107 °C	Measured
Flammability	Highly flammable.	Measured (as solid form) In contact with water no hazardous gasses were emitted.
Autoignition Temperature	258 °C	Measured
Explosive Properties	Not explosive	Predicted on basis of structure
Oxidising Properties	Not oxidising	Predicted on basis of structure

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

Hazard classification	*Hazard statement*
Flammable Solids	H228 – Flammable Solid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported into Australia in fragrance oils at ≤ 10% concentration.

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
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours & Fragrances (Australia) Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia in fragrance oils at concentrations ≤ 10%. The fragrance oils will be imported in ~208 L polypropylene-lined steel drums. Within Australia the drums will be transported by road to the warehouse for storage and later distributed to reformulation facilities by road. After reformulation the finished consumer products containing the notified chemical will be transported by road to retail stores.

USE
The notified chemical will be used as a fragrance ingredient in various cosmetic, personal care and household products. The final proposed concentration range of the notified chemical in end-use products will be ≤ 1%, with the exception of fine fragrances at ≤ 3%, hair spray at ≤ 2%, and deodorants at ≤ 0.5%.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. It will be imported at concentrations ≤ 10% in fragrance oils for reformulation into end-use cosmetics, personal care and household products. The reformulation process will likely vary depending on the type of end-use products and may involve both automated and manual transfer steps. However, in general it is expected that the reformulation processes will involve blending operations that will be highly automated and use closed systems with adequate ventilation, followed by automated filling of the reformulated products into containers of various sizes.

The finished cosmetic, personal care and household products containing the notified chemical at up to 3% concentration (typically ≤ 3.0% in fine fragrances, ≤ 2.0% in hair spray products, ≤ 0.5% in deodorants, and ≤ 1.0% in other domestic/household products) may be applied by hand, spray or through the use of applicators.

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)*
Mixing and compounding	4	250
Drum handling and cleaning	1 - 2	200 - 250
Plant operator - equipment maintenance	2	250
Quality control	1	250
Professional user – hairdressers, cleaners etc.	8	250

EXPOSURE DETAILS

Transport and warehouse workers

Transport and storage workers may come into contact with the notified chemical as a component of fragrance preparations (at concentrations ≤ 10%) only in the event of accidental rupture of the containers. The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective coveralls, chemical resistant gloves and safety glasses.

Formulation of end products

During reformulation, dermal, ocular and inhalation exposure of workers to the notified chemical (at ≤ 10% concentration) may occur during weighing and transfer stages, blending, quality control analysis, packaging of materials and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of PPE such as coveralls, goggles and impervious gloves, and adequate local ventilation or respiratory protection as required.

Beauty care and cleaning professionals

Exposure to the notified chemical in end-use products (at ≤ 3% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals are expected to follow good hygiene practices and may use PPE to minimise repeated exposure. If appropriate 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 through the use of a wide range of cosmetic and household products (at ≤ 3% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if the products are applied by spray.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012; Cadby *et al*., 2002; ACI, 2010; Loretz *et al*., 2006). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, a dermal absorption (DA) of 100% was assumed for the notified chemical (ECHA, 2017). For the inhalation exposure assessment, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr., 2009). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%, which accounts for a number of other exposure considerations (e.g., the amount ending up on the hair, as intended). A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (dermal exposure)

Product type	*Amount (mg/day)*	*Chemical concentration (%)*	*RF*	*Daily systemic exposure (mg/kg bw/day)*

Product type	*Amount*	*Chemical concentration*	*RF*	*Daily systemic exposure*
Body lotion	7,820	1.0	1	1.2219
Face cream	1,540	1.0	1	0.2406
Hand cream	2,160	1.0	1	0.3375
Deodorant (aerosol/ethanol)	1,500	0.5	1	0.1172
Fragrances	750	3.0	1	0.3516
Hair styling products	4,000	1.0	0.1	0.0625
Shower gel	18,670	1.0	0.01	0.02917
Hand wash soap	20,000	1.0	0.01	0.03125
Shampoo	10,460	1.0	0.01	0.01634
Hair conditioner	3,920	1.0	0.01	0.006125
Facial cleanser	800	1.0	0.01	0.00125
Total				**2.4154**

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	1.00	0.95	10	0.0341
Fabric softener	90	1.00	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	1.00	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1.00	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1.00	1980	1	0.01	0.007	0.0217
Total							**0.0245**

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	2.0	1	20	1	10	**0.0644**

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 chemical. This would result in a combined internal dose of 2.552 mg/kg bw/day for the notified chemical. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (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 chemical 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 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	LC50 > 4.94 mg/L/4 hour; low toxicity (respiratory irritation effects observed)
Skin irritation (*in vitro*) - EPIDERM™ human skin model	non-corrosive
Skin irritation (*in vitro*) - EPISKIN™ reconstructed human epidermis Model	non-irritating
Eye irritation (*in vitro*) - Bovine corneal opacity and permeability test	no prediction can be made
Eye irritation (*in vitro*) - Human cornea model test	irritating
Skin sensitisation (*in chemico*) – Direct peptide reactivity assay	not a category 1 skin sensitiser
Skin sensitisation (*in vitro*): ARE-Nrf2 luciferase test method	not a category 1 skin sensitiser
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Human, skin sensitisation – RIPT (5%)	no evidence of sensitisation
Human, skin sensitisation – RIPT (10%)	no evidence of sensitisation
Rat, combined repeated dose (dietary) with reproductive and developmental toxicity screening test	NOAEL (parental) = 259 mg/kg bw/day (males) and 293 mg/kg bw/day (females) NOAEL (developmental/reproductive) > 714 mg/kg bw/day (males) and > 790 mg/kg bw/day (females)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* Chromosome aberration test in human lymphocytes	non genotoxic

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemical were submitted. For dermal and gastrointestinal absorption, molecular weights below 100 g/mol are favourable for absorption and molecular weights above 500 g/mol do not favour absorption (ECHA, 2017). Dermal uptake is likely to be moderate to high if the water solubility is between 100 – 10,000 mg/L (ECHA, 2017). Dermal uptake through the epidermis is expected if the partition coefficient (log P) values are between -1 and 4 (ECHA, 2017). Gastrointestinal absorption and absorption across the respiratory tract are also likely to be high if the partition coefficient (log P) values are between -1 and 4 (ECHA, 2017). Absorption of the notified chemical through the skin, gastrointestinal tract and respiratory tract is expected based on the low molecular weight (168.28 g/mol), water solubility (0.496 g/L at 20 °C) and partition coefficient (log Pow = 3.67 at 20-25 °C) of the notified chemical.

Acute toxicity
The notified chemical was of low acute oral and dermal toxicity in rats.

In an acute inhalation toxicity study at a concentration of 4.94 mg/L, 3/10 animals died, with surviving animals showing bodyweight losses and red spots on the lungs. Additional effects in treated animals included increasingly severe dyspnea, lethargy, decreased breathing rate and general signs of discomfort (e.g. hypoactive behaviour, hunched posture, muscle weakness, ataxia, vocalisation, piloerection) during exposure.

Irritation and sensitisation
The notified chemical was found to be non-corrosive and not irritating to the skin based on *in vitro* studies.

The notified chemical was irritating to the eye based on an *in vitro* study conducted on a human cornea model with the potential to cause serious eye damage or irritation. An *in vitro* study conducted on bovine corneas

indicated that the notified chemical did not cause serious eye damage. When considered together, the notified chemical is expected to have the potential to cause serious eye irritation.

Respiratory irritation severe effects in treated animals were observed such as red spots on the lungs of survived animals and haemorrhages in the lungs of dead animals.

The notified chemical did not display any evidence of sensitisation potential when tested in and *in chemico* Direct Peptide Reactivity Assay (DPRA) and an *in vitro* ARE-Nrf2 Luciferase Test. Sensitising effects were not observed in a local lymph node assay or in human repeated-insult patch studies (at 5% and 10% concentration) following exposure to the notified chemical.

Repeated dose toxicity and reproductive/developmental toxicity
In a combined repeated dose (dietary) toxicity study with the reproduction/developmental toxicity screening test in rats a number of statistically significant changes in the clinical chemistry parameters were observed for both sexes given a nominal dose of 13,000 mg/kg diet or an actual dose of 714 mg/kg bw/day for males and 790 mg/kg bw/day for females. Therefore, the No Observed Adverse Effect Level (NOAEL) was set at the lower dose of 4,500 mg/kg diet (nominal) or 259 mg/kg bw/day for males and 293 mg/kg bw/day (actual dose) for females.

There were no adverse treatment related effects observed in any of the reproductive or developmental parameters measured. Subsequently the NOAEL is > 714 mg/kg bw/day for males and > 790 mg/kg bw/day for females.

Mutagenicity/Genotoxicity
The notified chemical was found to be not mutagenic in bacteria and did not induce chromosome aberrations in human lymphocytes.

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*
Specific target organ toxicity, single exposure (Category 2)	H371 – May cause damage to organs
Serious Eye Damage/Eye irritation (Category 2)	H319 – Causes serious eye irritation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is expected to be an eye irritant and adverse systemic effects were also noted following acute inhalation exposure and repeated oral exposure.

Transport, Storage and Reformulation
Exposure of workers to the notified chemical (at ≤ 10% concentration) may occur during transport and blending operations. The notified chemical is considered to be irritating. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

Provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE (impervious gloves, goggles, coveralls, and respiratory protection), the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical at ≤ 3% 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 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 chemical through the use of cosmetic and household products (containing the notified chemical at ≤ 3% in individual products). The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Local effects
The notified chemical is an eye irritant. However, given the low proposed use concentrations (≤ 3%) in cosmetic, personal care and household products, irritant effects are not expected.

Systemic effects
The potential systemic exposure (worst case using 100% dermal absorption) to the public from the use of the notified chemical in cosmetics and household products was estimated to be 2.552 mg/kg bw/day (see Section 6.1.2). Using the lowest NOAEL of 259 mg/kg bw/day reported for male rats derived from a combined repeated dose (dietary) with reproductive and developmental toxicity screening test, the margin of exposure (MOE) was estimated to be 101.5. 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 chemical at ≤ 1% in cosmetic, personal care and household products, with the exception of fine fragrances at ≤ 3%, hair spray at ≤ 2%, and deodorants at ≤ 0.5%, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance oil formulations for local reformulation into finished cosmetics, personal care 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 chemical is 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 chemical will be blended with other ingredients in the manufacture of cosmetics, personal care and household products within a fully enclosed environment. 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 chemical generated during reformulation include equipment wash water, empty import containers and spilt materials. These will be collected, recycled or released to on-site wastewater treatment facilities or sewers in accordance with local government regulations. Empty containers will be either recycled or disposed of to landfill.

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
Approximately 1% of the import volume of the notified chemical is expected to remain as residues in end-use containers (or up to 10 kg/yr). 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 result of the biodegradability study, the notified chemical is not considered readily biodegradable (0 to 1.5% in 28 days). For details of the environmental fate studies, please refer to Appendix C. The submitted study by the notifier has also indicated that the notified chemical is hydrolytically stable.

The half-life of the notified chemical in air is calculated to be 1.19 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA 2011). Therefore, in the event of release to the atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

In sewage treatment plants (STPs) a significant proportion of the notified chemical may partition to the water phase based on its moderate water solubility (496 mg/L) and low soil adsorption coefficient (log K_{OC} = 1.83 – 2.36) and be released to surface water. A proportion of the notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. The notified chemical residues in landfill and soils are expected to have high mobility based on its low soil adsorption coefficient. However, the notified chemical has low potential to bioaccumulate based on its n-octanol-water partition coefficient value (log P_{OW} < 4.2) and potential surface activity. In the aquatic and soil compartments, the notified chemical is expected to degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	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:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.75 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 18.73 µg/kg and 37.45 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 = 8.45 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 = 5.5 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 h ErC50 = 20 mg/L 72 h NOEC =1.9 mg/L	Harmful to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be toxic to fish and aquatic invertebrates, and harmful to algae. 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 2: Toxic to aquatic life". On the basis of acute toxicity data, NOEC value and lack of

biodegradability criteria, the notified chemical is formally classified as 'Chronic Category 2: Toxic to aquatic life with long-lasting effects".

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated from the most sensitive endpoint (NOEC) for algae. An assessment factor of 100 was used given three acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Alga)	1.9	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	19.00	µg/L

7.3. Environmental Risk Assessment

Insert the Risk Quotient Table (PEC/PNEC)

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	19	0.030
Q - Ocean	0.06	19	0.003

The Risk Quotients (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemical have been calculated to be < 1 for both river and ocean compartments indicating 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 not readily biodegradable, but is not considered to have bioaccumulation potential. 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

Freezing Point 23 - 60 °C

Method In house method
Remarks Determined using a differential scanning calorimeter
Test Facility CTL (2015)

Boiling Point 231± 0.5 °C at 102 kPa

Method OECD TG 103 Boiling Point
EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks Determined using a differential scanning calorimeter
Test Facility Envigo (2017a)

Density 958 kg/m^3 at 20.0 ± 1.0 °C

Method OECD TG 109 Density of Liquids and Solids
EC Council Regulation No 440/2008 A.3 Relative Density
Remarks Determined using a gas comparison pycnometer
Test Facility Envigo (2017a)

Vapour Pressure 16.84 Pa at 20 °C

Method OECD TG 104 Vapour Pressure
EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks Determined using a U-tube manometer
Test Facility CTL (2015)

Water Solubility 496 mg/L at 20 °C

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

Hydrolysis as a Function of pH Hydrolytically stable at pH 4,7, and 9

Method OECD TG 111 Hydrolysis as a Function of pH and EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ (years)*
4	50	Not determined
7	50	Not determined
9	50	Not determined

Remarks Analysis of samples for the notified chemicals was performed by High performance liquid chromatography (HPLC). A nominal concentration of 200 mg/L was prepared in demineralised water + 2 % acetonitrile. The test was carried out at 50 °C with samples taken after 5 days (120 hours). No signs of hydrolysis of the test item were observed after 120 h at 50 °C at pH 4, 7 and 9. Therefore, the notified chemical is considered hydrolytically stable.
Test Facility LAUS (2016a)

Partition Coefficient (n-octanol/water) log Pow = 3.68 at 20 to 25 °C

Method EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks Shake Flask Method
Test Facility CTL (2015)

Surface Tension **48.5mN/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: 1g/L.
Test Facility	Envigo (2017a)

Adsorption/Desorption log K_{oc} = 1.83 and 2.36 at 25 °C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (KOC) on Soil and on Sewage Sludge using High Performance Liquid Chromatography.
Remarks	HPLC method
Test Facility	LAUS (2016b)

Flash Point 107 °C at 102.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Closed cup equilibrium method
Test Facility	Envigo (2017b)

Flammability Highly flammable

Method	Compatible with EC Council Regulation No 440/2008 A.10 Flammability (Solids)
Remarks	The test item was formed into a 'rope'250 mm long with a cross section of approximately 1 cm^2. The 'rope' burnt with a yellow/orange flame that emitted black fumes with a burning time of 8 sec. The test item propagated combustion over 100 mm in under 45 seconds
Test Facility	Envigo (2017b)

Autoignition Temperature 258 ± 5 °C

Method	Compatible with EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Method was based on, Anon (1987), Electrical Apparatus for Explosive Gas Atmospheres. Part 4: Method of Test for Ignition Temperature. IEC Publications 79-4, P1-19.
Test Facility	Envigo (2017b).

Explosive Properties

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	No structural alerts within the chemical structure of the test item
Test Facility	Envigo (2017b)

Oxidizing Properties

Method	EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids)
Remarks	No structural alerts within the chemical structure of the test item
Test Facility	Envigo (2017b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure EC Council Regulation No 440/2008 B.1 bis Acute toxicity (oral) fixed dose method
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	GLP compliant No deviations from the protocol

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Signs of systemic toxicity included hunched posture, ataxia, tiptoe gait, laboured respiration and/or decreased respiratory rate, piloerection, dehydration, loss of righting reflex and lethargy. All effects had resolved by the day 3 observation.
Effects in Organs	No effects reported
Remarks - Results	No deaths occurred at any dose tested and all animals appeared normal three days after dosing. All animals made the expected body weight gains.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Envigo (2017c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/ Wistar Crl:WI (Han) (outbred, SPF-Quality)
Vehicle	Propylene glycol
Type of dressing	Occlusive
Remarks - Method	GLP compliant. No deviations from the study protocol

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Focal erythema, erythema maculate, scales and/or scabs were seen at the treatment sites.
Signs of Toxicity - Systemic	Lethargy, flat posture, hunched posture, uncoordinated movements, quick breathing, slow breathing, shallow respiration, piloerection, chromodacryorrhoea, ptosis, red secretion of the vagina and/or hypothermia.

Effects in Organs	No effects were detected.
Remarks - Results	No deaths occurred in males or females. All animals made the expected body weight gains.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	WIL (2016)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity
Species/Strain	Wistar outbred (Crl:WI(Han)) rats
Vehicle	ethanol
Method of Exposure	Oro-nasal exposure
Exposure Period	4 hours
Physical Form	solid aerosol
Particle Size	2.47 μm and 2.59 μm
Remarks - Method	GLP compliant No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration <mg/L/>*		*Mortality*
		Nominal	*Actual*	
1	5M, 5F	34.81	4.94	3/10

LC50	> 4.94 mg/L /4 hours
Signs of Toxicity	One male animal and two female animals died during the study. All treated animals showed increasingly severe dyspnea, lethargy, decreased breathing rate and general signs of discomfort (e.g. hypoactive behaviour, hunched posture, muscle weakness, ataxia, vocalisation, piloerection) during exposure.
Effects in Organs	In the three animals that died during the study air filled gastrointestinal tract and haemorrhages in the lungs were observed. In animals that survived to the scheduled necropsy red spots on one or more lung lobes were observed in 3 animals.
Remarks - Results	Surviving animals showed a 3-8% bodyweight loss the day after exposure.
CONCLUSION	The notified chemical is of low acute toxicity via inhalation.
TEST FACILITY	Triskelion (2016a)

B.4. 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 compliant Duplicate tissues, negative and positive controls were treated with the test item for exposure periods of 3 and 60 mins. The notified chemical directly reduced MTT and therefore, additional non-viable tissues were incorporated into the testing.

RESULTS

Test material	Mean OD_{562} of duplicate tissues (± SD)		Relative mean viability (%)	
	3 min exposure	60 min exposure	3 min exposure	60 min exposure
Negative control	2.014 (± 0.016)	1.889 (± 0.108)	100	100
Test substance	1.998 (± 0.205)	2.127 (± 0.047)	99.2	112.6
Positive control	0.088 (± 0.018)	0.084 (± 0.008)	4.3	4.4

OD = optical density; SD = standard deviation

Remarks - Results: The positive and negative controls performed as expected.

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

TEST FACILITY: Envigo (2016)

B.5. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 439 Reconstructed Human Epidermis test -EPISKIN- Dermal Irritation
EC Council Regulation No 761/2009 B.46 Reconstructed Human Epidermis Model Test- Acute Toxicity (Skin Irritation)

Species/Strain: Reconstructed human epidermis cultures
Vehicle: Not mentioned
Observation Period: 42 hours
Remarks - Method: GLP compliant
No significant protocol deviations

RESULTS

Test material	Mean OD_{562} of triplicate tissues	Relative mean Viability (%)	SD of relative mean viability (%)
Negative control	0.853	100	6.9
Test substance	0.511	59.9	17.2
Positive control	0.119	14.0	6.8

OD = optical density; SD = standard deviation

Remarks - Results: The test substance showed > 50% relative mean viability, not requiring it to be classified as a skin irritant.

The positive and negative controls performed as expected.

CONCLUSION: The notified chemical is not-irritating to the skin.

TEST FACILITY: Envigo (2017d)

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 compliant.
The neat test item was applied for 240 mins as to a concentration of 20 % w/v in saline could not be formulated.

The positive control in vitro irritancy score (IVIS) was not within the range of 66.9 to 101.4 and therefore not within the positive control acceptance criterion. However, the study authors suggest that this is not expected to affect the integrity or validity of the study as the score was not significantly higher.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Negative control	1.7 (± 1.2)	0.040 (± 0.014)	2.3 (± 1.4)
*Test substance**	1.5 (± 1.3)	2.275 (± 0.048)	35.7 (± 2.0)
*Positive control**	85.3 (± 8.2)	1.554 (± 0.335)	108.6 (± 13.2)

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

Remarks - Results: The negative control performed as expected.

The IVIS for the test substance was 35.7. As this value was between 3 and 55, no prediction regarding the eye irritation potential of the notified chemical can be made.

CONCLUSION: No prediction of the eye irritation can be made.

TEST FACILITY: Envigo (2017e)

B.7. Irritation – eye (*in vitro*)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 492 Reconstructed Human Cornea - like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage

Vehicle: None

Remarks - Method: GPL compliant.
No significant protocol deviations.

RESULTS

Test material	*Mean Absorbance of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.703	100
Test substance	0.071	4.2
Positive control	0.303	17.8

OD = optical density

Remarks - Results: The positive and negative controls performed as expected.

CONCLUSION: The notified chemical was considered to be irritating to the eye under the conditions of the test.

TEST FACILITY: Envigo (2017f)

B.8. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 442C *In Chemico* Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA) (2015)

Vehicle: Acetonitrile

Remarks - Method: The test substance and controls (cinnamic aldehyde) were prepared in

acetonitrile (100 mM stock solution). Solvent reference controls were setup and used in parallel to sample preparation in order to verify the validity of the test run. Peptide standards were prepared at concentrations of 0.534-0.0167 mM in acetonitrile and phosphate or ammonium acetate buffer. The test substance was incubated in dark at room temperature with the peptide solutions for 24 h. The ratios of test substance: peptides were 1:10 cysteine peptide and 1:50 lysine peptide. After incubation, peptide depletion was monitored by HPLC coupled with a photodiode array detector set at 220 nm.

RESULTS

Sample	*Cysteine Peptide Depletion (% ± SD)*	*Lysine Peptide Depletion (% ± SD)*
Vehicle	0.00*	0.00*
Test Substance	6.4 (± 0.3)	5.1 (± 0.3)
Control – Cinnamic Aldehyde	81.8 (± 0.1)	63.0 (± 3.6)

* – normalised to 100%; SD = Standard Deviation

Remarks - Results

The reactivity of the test substance with the peptides measured as depletion of peptides was less than the percentage (mean of 6.38% for cysteine and lysine or 13.89% for cysteine on its own) required for categorisation as a category 1 sensitiser.

The positive controls and references fulfilled all quality criteria confirming the validity of the test.

CONCLUSION

The test substance was not considered a skin sensitiser.

TEST FACILITY

IIVS (2015a)

B.9. Skin sensitisation

TEST SUBSTANCE

Notified chemical

METHOD

Similar to OECD TG 442d *In Vitro* Skin Sensitisation: ARE-Nrf2 Luciferase Test Method (2015)

Vehicle

Dimethylsulfoxide (DMSO)

Remarks - Method

No significant deviations from the OECD test guideline. Promega ONE-Glo™ Luciferase Assay System was used.

A 200 mM stock solution of test substance was prepared in dimethyl sulphoxide (DMSO) and a set of twelve master solutions were prepared in DMSO from this stock solution (0.978, 1.95, 3.91, 7.81, 15.6, 31.3, 62.5, 125, 250, 500, 1000 and 2000 µM). DMSO and cinnamic aldehyde (4, 8, 16, 32, and 64 µM) were used as negative and positive controls respectively. Three independent assays were conducted. Each assay included a set of 4 plates (3 for gene induction, 1 for cytotoxicity assessment). Maximal induction of luciferase activity was measured at 565 nm (relative light units), while maximal gene induction (cytotoxicity assessment) was measured using absorption values at 570 nm.

A test substance is predicted to have sensitisation potential if:
- the EC1.5 value is < 1,000 µM in at least 2 of 3 repetitions,
- cellular viability was > 70% at the lowest concentration with a gene induction > 1.5,
- there was an apparent overall dose response which was similar between repetitions.

The mean values for cell viability and luciferase induction were provided. Individual values from the replicate experiments were not included in the

report.

RESULTS

Sample	*Mean EC1.5 (μM)*	*Mean IC50 (μM)*	*I_{max}*
Test substance	> 2,000	1089.96	1.09
Positive Control	8.92	> 64	not provided

EC1.5 - concentration for an induction of luciferase activity 50% above vehicle control
IC50 - concentration leading to 50% cell viability compared to vehicle control
I_{max} – maximal induction

Remarks - Results

The lowest concentration of test substance that produced gene induction above 1.5 was 1089.96 μM, and the EC1.5 value was greater than 2,000 μM. The study authors reported that the test substance did not meet the criteria for categorisation as a potential sensitiser.

The positive and vehicle controls were reported to have performed as expected.

CONCLUSION

The substance was not considered a Category 1 skin sensitiser.

TEST FACILITY

IIVS (2015b)

B.10. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE

Notified chemical

METHOD

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

Species/Strain: Mouse/female CBA/CAOlaHsd
Vehicle: Acetone/olive oil 4:1
Preliminary study: Yes
Positive control: α-Hexylcinnamaldehyde (97.3 %) at 25 % concentration v/v in acetone/olive oil 4:1.
Remarks - Method: GLP compliant
No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	1025.89	-
10% w/w	5 F	1389.60	1.35
25 % w/w	5F	1500.90	1.46
50 % w/w	5F	1198.20	1.17
Positive Control			
25 % v/v	5F	5826.31	5.68

Remarks - Results

There were no deaths or any signs of systemic toxicity at any concentration during the study. All animals made the expected gains in body weight.

Ear thickness was also measured before after exposure and no significant changes were noted at a concentration of 50%.

Positive and negative controls performed as expected.

Conclusion

There was no evidence of induction of a lymphocyte proliferative response

indicative of skin sensitisation to the notified chemical.

Test Facility: Envigo (2017g)

B.11. Skin sensitisation – human volunteers (HRIPT-1)

TEST SUBSTANCE: Notified chemical (at 5% concentration)

METHOD
Study Design: Repeated insult patch test with challenge (RIPT) - Shelanski Method
Induction Procedure: 113 subjects participated in the study. The test material was applied under an occlusive patch to the upper back of each subject and was allowed to remain in direct skin contact for a period of 24 hours. Patches infused with 0.15 mL of the test substance were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during induction period. The sites were graded for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday.

Rest Period: 10 -21 days

Challenge Procedure: Challenge patches were applied to previously untreated test sites on the back, approximately 10 to 21 days after the induction phase. After 24 hours, the patches were removed and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 to 72 hours after application.

Study Group: 90 F, 23 M; age range 19- 70 years
Vehicle: EtOH:DEP (1:3)
Remarks - Method: Occluded. The test substance was spread on a 3.63 cm × 3.63 cm patch.

RESULTS
Remarks - Results: 107/113 subjects completed the study, five subjects discontinued the study for reasons unrelated to the test material and one subject was discontinued due to reaction to multiple products.

Mild erythema was observed in 2 subjects after the first induction, this declined to barely perceptible erythema after the second induction while the other subject had no sign of irritation. A third individual had an isolated incidence of barely perceptible erythema after the third induction. No other signs of irritation were seen in any of the subjects during the induction phase. During the challenge phase one subject had mild erythema at the 48 hour observation only. No other signs of irritation were seen during the challenge.

CONCLUSION: The notified chemical was non-sensitising under the conditions of the test.

TEST FACILITY: CRL (2016)

B.12. Skin sensitisation – human volunteers (HRIPT-2)

TEST SUBSTANCE: Notified chemical (at 5% and 10% concentration)

METHOD
Study Design: Repeated insult patch test with challenge (RIPT) - Shelanski Method
Induction Procedure: 113 subjects participated in the study. The test material was applied under an occlusive patch to the upper back of each subject and was allowed to remain in direct skin contact for a period of 24 hours. Patches infused with 0.15 mL of the test substance were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during induction period. The sites were graded for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday.

	Rest Period: 10 -21 days Challenge Procedure: Challenge patches were applied to previously untreated test sites on the back, approximately 10 to 21 days after the induction phase. After 24 hours, the patches were removed and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 to 72 hours after application.
Study Group	90 F, 23 M; age range 19- 70 years
Vehicle	EtOH:DEP (1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm × 3.63 cm patch.
RESULTS	
Remarks - Results	108 subjects completed the study; five subjects discontinued the study for reasons unrelated to the test material. No irritation was observed in any of the test subjects at the sites where a concentration of 5% had been applied. At a concentration of 10% irritation was seen in only 1 test subject, and was limited to barely perceptible erythema at the observation 48 hours after challenge and mild erythema at the observation 72 hours after challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2017)

B.13. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species/Strain	Rat/Wistar IGS (Crl:WI(Han)))
Route of Administration	Oral –diet
Exposure Information	Total exposure days: Males 14 days pre-mating and then till sacrifice after ≥ 28 days of exposure, Females from 14 days pre-mating, during mating, gestation and then up to day 4 of lactation. Dose regimen: 7 days per week
Vehicle	Diet
Remarks - Method	GLP compliant No significant protocol deviations. The dose selection was based on the results of a 14-day dose range finding study at doses up to 15,000 mg/kg diet, where increased kidney and liver weights and decreased body weights and food consumption were observed at the maximum dose (Triskelion, 2016b).

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (mg/kg diet)	*Actual (mg/kg bw/day)*	
control	12 M; 12 F	0	0	0/24
low dose	12 M; 12 F	1,000	Male pre-mating: 62.46 Male post-mating: 55.62 Female pre-mating: 71.57 Female gestation: 71.86 Female lactation: 109.87 Male average: 59 Female average: 72	0/24

mid dose	12 M; 12 F	4,500	Male pre-mating: 267.97 Male post-mating: 250.19 Female pre-mating: 304.05 Female gestation: 292.87 Female lactation: 493.37 Male average: 259 Female average: 293	0/24
high dose	12 M; 12 F	13,000	Male pre-mating: 697.29 Male post-mating: 731.49 Female pre-mating: 789.23 Female gestation: 796.03 Female lactation: 1230.84 Male average: 714 Female average: 790	0/24

Mortality and Time to Death
All animals survived to the scheduled necropsy.

Clinical Observations
No treatment-related clinical signs were observed. No adverse effects in neurobehaviour were indicated in animals exposed to the test item.

Male animals in the high-dose group showed statistically significantly lower mean body weights during the pre-mating and the post-mating periods. During the gestation and lactation periods mean bodyweights of the high-dose females showed a statistically significantly decrease. Animals of both sexes in the mid and high dose groups showed statistically significant decreases in food consumption.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
In the mid- and high-dose male animals, statistically significantly increases in concentrations of creatinine and urea were observed. A statistically significantly decrease in plasma glucose levels was also noted in high-dose males.

In high-dose females, concentrations of total protein, cholesterol and phospholipids showed statistically significantly increases, while the ratio albumin/globulin showed a statistically significant decrease.

There were no treatment related adverse effects in the measured haematological parameters.

Effects in Organs
In high-dose males, the relative weight of the epididymides and testis showed statistically significant increases and in high-dose females, the absolute weight of the heart showed a statistically significant decrease. There were no treatment related abnormalities observed during the macroscopic examination.

Microscopic examination showed a range of nephrotoxic effects related to the accumulation of α2-microglobulin in the male kidneys. Such effects are rat specific and not usually relevant to human toxicity (Swenberg, 1993).

Reproductive and developmental findings
No effects on fertility and reproductive performance were observed. No effect was observed on the mean number of corpora lutea and implantation sites and pre-implantation loss was not affected by the treatment. No treatment-related effects were observed on prenatal loss and perinatal loss. No treatment-related effects on the mean number of pups delivered, mean pup weights and the sex ratio were observed.

Remarks – Results
Animals in the high dose group showed statistically significant decreases in body weights and also food consumption. As the test substance was administered in the diet these changes may be related to the palatability of substance in the feed rather than systemic toxicity.

A number of statistically significant changes in the clinical chemistry parameters were observed for both sexes given a nominal dose of 13,000 mg/kg diet or an actual dose of 714 mg/kg bw/day for males and 790 mg/kg bw/day for females. Therefore, the No Observed Adverse Effect Level (NOAEL) was set at the lower dose of

4,500 mg/kg diet (nominal) or 259 mg/kg bw/day for males and 293 mg/kg bw/day (actual dose) for females.

There were no adverse treatment related effects observed in any of the reproductive or developmental parameters measured. Subsequently the NOAEL is > 714 mg/kg bw/day for males and > 790 mg/kg bw/day for females.

CONCLUSION
The NOAEL for toxicity in the parental animals was established as 259 mg/kg bw/day for males and 293 mg/kg bw/day for females based on adverse effects observed in the clinical chemistry parameters at the higher dose.

The NOAEL for reproductive and developmental toxic was established as > 714 mg/kg bw/day in males and > 790 mg/kg bw/day in females.

TEST FACILITY Triskelion (2016c).

B.14. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test
Plate incorporation procedure/Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbital/5,6-benzoflavone-induced (Aroclor 1254) rat liver
Concentration Range in Main Test	a) With metabolic activation: 39 to 5000 µg/plate b) Without metabolic activation: 19 to 5000 µg/plate
Vehicle	DMSO
Remarks - Method	GLP compliant The first test was repeated with the *S. typhimurium* strains TA1535, TA1537 and TA100 in the absence of metabolic activation due to cytotoxicity. The second test was repeated for the *E. coli* strain in the absence of metabolic activation as the negative control was outside the acceptable range.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1a	≥ 1667	≥ 1667	> 5000	negative
Test 1b		≥ 1500	> 1500	negative
Test 2a		≥ 1250	> 1250	negative
Test 2b		≥ 2500	> 2500	negative
Present				
Test 1	≥ 1667	≥ 1667	> 5000	negative
Test 2		≥ 1250	> 1250	negative

Remarks - Results The test substance did not induce a more than 2-fold and/or dose related increase in the mean number of revertant colonies compared to the background spontaneous reversion rate observed with the negative control.

Positive and negative controls performed as expected confirming the validity of S9-mix and the test system.

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

TEST FACILITY Triskelion (2015a)

B.15. Genotoxicity – *in vitro*

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 fraction from phenobarbital/5,6-benzoflavone-induced (Aroclor 1254)) rat liver
Vehicle	DMSO
Remarks - Method	GLP compliant No significant protocol deviations In the first test both in the absence and presence of metabolic activation the mitotic index dose response results did not meet the test criteria and subsequently test 1 was not evaluated for chromosomal aberrations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*
Absent			
Test 1	0, 2.0, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000	4 hr	24 hr
Test 2a	0*, 50, 75, 100, 125*, 150, 175*, 200*, 250	4 hr	24 hr
Test 2b	0*, 25, 50, 75*, 100, 125*, 150, 175*, 200, 250, 300	24 hr	24 hr
Present			
Test 1	0, 2.0, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000	4 hr	24 hr
Test 2	0*,50, 100, 150*, 200, 250*, 300*, 350	4 hr	24 hr

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 250	> 1000	negative
Test 2a	≥ 200	> 250	negative
Test 2b	≥ 51	> 120	negative
Present			
Test 1	≥ 500	> 1000	negative
Test 2	≥ 300	> 350	negative

Remarks - Results

No statistically significant or biologically relevant increase in the number of cells with chromosome aberrations was observed in the presence or absence of metabolic activation.

Positive and negative controls performed as expected.

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

TEST FACILITY Triskelion (2015b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	Activated sludge
Exposure Period	28 day
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	-0.93	5	-
8	-0.59	8	57.04
14	-0.17	14	72.01
23	-2.54	23	-
28	1.53	28	-

Remarks - Results	All validity criteria of the test guideline were satisfied. The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 14 days (72%). Therefore, the tests indicate the suitability of the inoculums. The toxicity test showed no toxic effects of the test substance to the micro-organisms at the test concentration of 2 mg/L. The degree of degradation of the test substance after 28 days was 1.53%.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	SXZD (2016a)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Manometric Respirometry Test
Inoculum	Treated effluent
Exposure Period	28 day
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	0	4	0
7	0	7	22
14	0	14	75

21	0	21	77
28	0	28	78

Remarks - Results

All validity criteria of the test guideline were satisfied.

The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 14 days (78%). Therefore, the tests indicate the suitability of the inoculums. The toxicity test showed no toxic effects of the test substance to the micro-organisms at the test concentration of 2 mg/L. The test item attained 0% biodegradation after 28 days and therefore cannot be considered to be readily biodegradable under the strict terms and conditions of OECD Guideline 301F.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY Envigo (2017h)

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	*Gobiocypris rarus*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	60 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatograph mass spectrometer
Remarks – Method	The fish were exposed to the control and test solutions for a period of 96 hours with renewal of the test solution every 24 hours. Daily renewal of exposure medium for controls and test solutions was performed every 24 hours.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality (% cumulative mortality)*				
Nominal	*Actual*		*3 h*	*6 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
31	32	7	0	0	0	0	0
62.5	62	7	0	0	0	1	1
125	126	7	0	0	1	2	3
250	244	7	0	0	2	3	5
500	505	7	0	2	4	5	6

LC50	8.45 mg/L at 96 hours
NOEC (or LOEC)	Not reported
Remarks – Results	All validity criteria of the test guideline were satisfied. All validity criteria of the test guideline were satisfied, except there was evidence that the test substance was not satisfactorily maintained. Therefore, results were based on measured concentrations. The 96 h LC50 for fish was determined to be 8.45 mg/L based on mean measured concentrations.

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

TEST FACILITY SXZD (2016b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static test conditions
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	Not measured
Analytical Monitoring	Gas chromatography with mass spectrometry (GC-MS)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. pH: 7.7 for all treatments and control at 0 and 48 hours. DO: 8.6 – 8.9 mg/L for all treatments and control at 0 and 48 hours. Temperature: 21 – 22 ºC for all treatments and control at 0 and 48 hours.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
1.8	1.40	20	0	0
3.2	2.55	20	0	0
5.6	4.89	20	0	3
10	9.49	20	18	20
18	17.7	20	20	20
32	31.5	20	20	20
56	51.1	20	20	20

EC50	5.5 mg/L at 48 hours
NOEC	0.56 at 48 hours
Remarks - Results	All validity criteria of the test guideline were satisfied. The system was static and conditions of the test were maintained, and test solutions not renewed. The 48 h EC50 and NOEC for Daphnia were determined to be 5.5 mg/L and 0.56 mg/L, respectively, based on 0-Hour measured test concentrations only. Measured concentrations were relatively stable over the test period.
CONCLUSION	The notified chemical is considered to be toxic to aquatic invertebrates
TEST FACILITY	Envigo (2017i)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE

METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0 – 100 % v/v Mean measured: 0.87 – 84 % v/v
Auxiliary Solvent	None
Water Hardness	Not measured
Analytical Monitoring	Gas chromatography with mass spectrometry (GC-MS)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. pH: 7.6 – 8.8 for all treatments and control at 0 and 72 hours.

RESULTS

Biomass (Yield)		*Growth (Rate)*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
6.5 (6.3 – 6.7)	1.9	20 (16 – 24)	1.9

Remarks - Results	All validity criteria of the test guideline were satisfied. The actual concentrations of the test item were measured at the start of the test period. A decline in measured test concentration was observed at 72 hours to between 0.76 and 75.7 mg/L (71% to 84% of the 0-Hour measured test concentrations). Therefore the results were based on the geometric mean measured test concentration. The 72 h EC50 (growth) and NOEC (growth) for algae were determined to be 20 mg/L and 1.9 mg/L, respectively, based on mean measured concentrations.
CONCLUSION	The notified chemical is considered to be harmful to algae.
TEST FACILITY	Envigo (2017j)

BIBLIOGRAPHY

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

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

CTL (2015) Phys/ Chem Testing on a Sample of FRET 11-0571-01 (Study No. GLP113231R1V2/2015, July, 2015). Southampton, United Kingdom, Chilworth Technology Limited (Unpublished report submitted by the notifier)

CRL (2016) Repeated Insult Patch test (RIPT) – Shelanski Method (Study No. CRL08216-1, May, 2016). Piscataway, New Jersey, USA, Clinical Research Laboratories, LLC. (Unpublished report submitted by the notifier).

CRL (2017) Repeated Insult Patch test (RIPT) – Shelanski Method (Study No. CRL2017-0034, March, 2017). Piscataway, New Jersey, USA, Clinical Research Laboratories. (Unpublished report submitted by the notifier).

Earnest CW 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 (2017) Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c: Endpoint specific guidance, June 2017, version 3.0. European Chemicals Agency, https://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf

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.

Envigo (2016) FRET 11-0571: *In vitro* EPIDERM™ Skin Corrosion Test (Study No. PT69CF, December, 2016). Derbyshire, U.K., Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017a) FRET 11-0571: Determination of General Physico-Chemical Properties (Study No. SW43RG, January, 2017). Shardlow, United Kingdom, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017b) FRET 11-0571: Determination of Hazardous Physico-Chemical Properties (Study No. XF12FN, June, 2017). Shardlow, United Kingdom, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017c) FRET 11-0571: Acute Oral Toxicity in the Rat - Fixed Dose Method (Study No. CS10DK, February, 2017). Derbyshire, U.K., Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017d) FRET 11-0571: Determination of Skin Irritation Potential using the EPISKIN™ Reconstructed Human Epidermis Model (Study No. XM28FG, January, 2017). Derbyshire, U.K., Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017e) FRET 11-0571: The Bovine Corneal Opacity and Permeability (BCOP) Assay (Study No. RB70NY, April, 2017). Derbyshire, U.K., Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017f) FRET 11-0571: *In vitro* Eye Irritation test: Human Cornea Model Test (Study No.1818900, June, 2017). Rossdorf, Germany, Envigo CRS GmbH (Unpublished report submitted by the notifier).

Envigo (2017g) FRET 11-0571: Local Lymph Node Assay in the Mouse – Individual Method (Study No. BY21GC, March, 2017). Derbyshire, U.K., Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017h) FRET 11-0571: Assessment of Ready Biodegradability; Manometric Respirometry Test (Study No. MQ95CQ, February, 2017). Shardlow, United Kingdom, Envigo Research Limited (Unpublished report submitted by the notifier)

Envigo (2017i) FRET 11-0571: Daphnia sp., 48-Hour Acute Immobilization Test (Study No. WF53LM, June, 2017). Shardlow, United Kingdom, Envigo Research Limited (Unpublished report submitted by the notifier)

Envigo (2017j) FRET 11-0571: Algal Growth Inhibition Test (Study No. RN78GP, May, 2017). Shardlow, United Kingdom, Envigo Research Limited (Unpublished report submitted by the notifier)

IIVS (2015) Direct Peptide Reactivity Assay (DPRA) (Study No. 14AQ07-AQ13.180000, August, 2015). Gaithersburg, Maryland, United States of America, Institute for In Vitro Sciences, Inc. (Unpublished report submitted by the notifier)

IIVS (2015) Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE-Reporter Cell Line Keratinosens (Study No. 14AQ07-AQ13.170001, April, 2015). Gaithersburg, Maryland, United States of America, Institute for In Vitro Sciences, Inc. (Unpublished report submitted by the notifier)

LAUS (2016a) Determination of pH-dependent Hydrolysis in Water of FRET 11-0571 according to OECD Guideline 111 and EU Method C.7 (Study No. 16031708G916, December, 2016). Kirrweiler, Germany, LAUS GmbH (Unpublished report submitted by the notifier)

LAUS (2016b) Estimation of the adsorption coefficient on soil and on sewage sludge of FRET 11-0571 using HPLC according to OECD 121 resp. EU C.19 (Study No. 16031708G923, December, 2016). Kirrweiler, Germany, LAUS GmbH (Unpublished report submitted by the notifier)

Loretz L, Api AM, Barraj L, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YHL, Re T, Renskers K, Scrafford C, Vater S (2006) Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food and Chemcial Toxicology, **44**:2008-2018.

NTC (2017) Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), Edition 7.5, National Transport Commission, Commonwealth of Australia

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

SCCS (2012) The SCCS's notes of guidance for the testing of cosmetic substances and their safety evaluation (8th revision), European Commission - Scientific Committee on Consumer Safety.

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

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

SWA (2015) Code of Practice: Spray Painting and Powder Coating, Safe Work Australia, https://www.safeworkaustralia.gov.au/doc/model-code-practice-spray-painting-and-powder-coating.

Swenberg J (1993) α_{2U}-Globulin Nephropathy: Review of the Cellular and Molecular Mechanisms Involved and Their Implications for Human Risk Assessment. Environmental Healt Perspectives Supplements, **101**(Supp. 6):39-44.

SXZD (2016a) Ready Biodegradability Test of FRET 11-0571 (Study No. 2016-094-01-02, June, 2016). Suzhou City, China, Suzhou Xishan Zhongke Drug R&D Co., Ltd. (Unpublished report submitted by the notifier)

SXZD (2016b) Fish, Acute Toxicity Test for FRET 11-0571 (Study No. 20 16-094-01-0 I, October, 2016). Suzhou City, China, Suzhou Xishan Zhongke Drug R&D Co., Ltd. (Unpublished report submitted by the notifier)

Triskelion (2015a) Bacterial reverse mutation test with FRET 11-0571 (Study No. 20705/02, May, 2015). Zeist, Netherlands, Triskelion B.V. (Unpublished report submitted by the notifier)

Triskelion (2015b) Chromosomal aberration test with FRET 11-0571 in cultured human lymphocytes (Study No. 20702/02, June, 2015). Zeist, Netherlands, Triskelion B.V. (Unpublished report submitted by the notifier)

Triskelion (2016a) Acute (4-hour) inhalation toxicity study with FRET 11-0571 in rats (Study No. 20787, October, 2016). Zeist, Netherlands, Triskelion B.V. (Unpublished report submitted by the notifier)

Triskelion (2016b) A 14-day dose range finding study with FRET 11-0571 in rats (Study No. 20785/01, May, 2016). Zeist, Netherlands, Triskelion B.V. (Unpublished report submitted by the notifier)

Triskelion (2016c) Combined oral repeated dose toxicity study and reproduction/developmental toxicity screening test in rats with FRET 11-0571(Study No. 20785/02, November, 2016). Zeist, Netherlands, Triskelion B.V. (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) Estimations Programs Interface (EPI) SuiteTM for Microsoft Windows®, v 4.10. United States Environmental Protection Agency, Washington DC, USA. Available at http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

WIL (2016) Assessment of Acute Dermal Toxicity with FRET 11-0571 in the Rat (Study No. 514040, June, 2016). Hertogenbosch, Netherlands, WIL Research Europe B.V. (Unpublished report submitted by the notifier)