File No: LTD/1991

November 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexane, 2-ethoxy-1,3-dimethyl-, (1α,2α,3α)-

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/1991	International Flavours and Fragrances (Australia) Pty Ltd	Cyclohexane, 2-ethoxy-1,3-dimethyl-, (1α,2α,3α)-	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Flammable liquids (Category 3)	H226 – Flammable liquid and vapour
Skin sensitisation (Category 1B)	H317 - May cause an allergic skin reaction

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:
  – Skin Sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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

Health Surveillance

- As the notified chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation:
  - Enclosed, automated processes, where possible
  - Adequate local exhaust ventilation

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

- 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:
  - Coveralls
  - Impervious gloves

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

- If products and mixtures containing the notified chemical is 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 physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum for the notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 1% in deodorant, hand cream, and hairstyling (non-spray) products; 1.85% in fine fragrances; 2% in other leave-on cosmetic products; 2.5% in hairspray and household cleaning products; 5% in rinse-off cosmetic products or 10% in air-care products;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
International Flavours and 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: hydrolysis as a function of pH, dissociation constant, and flammability.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
China and USA

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Anomix

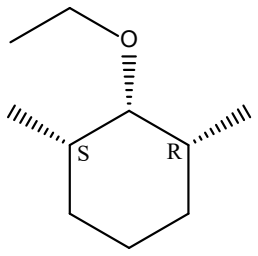
CAS NUMBER
2119667-72-8

CHEMICAL NAME
Cyclohexane, 2-ethoxy-1,3-dimethyl-, (1α,2α,3α)-

OTHER NAME
2,6-Dimethylcyclohexyl ethyl ether

MOLECULAR FORMULA
$C_{10}H_{20}O$

STRUCTURAL FORMULA



Relative stereochemistry

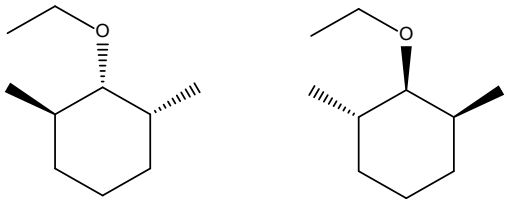
MOLECULAR WEIGHT
156.27 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
~92%

IMPURITIES
The following two isomers of the notified chemical are present at ~6%:



ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	174 °C at 102.7 kPa	Measured
Density	846 kg/m^3 at 20 °C	Measured
Vapour Pressure	0.342 kPa at 25 °C	Measured
Water Solubility	7.09 x 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemical is not expected to hydrolyse significantly in the environmental pH of 4-9
Partition Coefficient (n-octanol/water)	log Pow = 3.97 at 25 °C log Pow = 4.67 and 5.24 (HPLC method)	Measured
Surface Tension	70.3 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.87 and 3.12	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	47 ± 2 °C at 100.3 kPa	Measured
Flammability	Flammable liquid (Category 3)	Based on measured flash point
Autoignition Temperature	194 ± 5 °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. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable liquids (Category 3)	H226 – Flammable liquid and vapour

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported as a component of finished fragrance oil at ≤ 10% concentration for local reformulation into cosmetic and household products.

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

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

PORT OF ENTRY
Melbourne

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

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of fragrance oils in 208 L polypropylene-lined steel drums by sea. Within Australia the drums will be transported by road to the warehouse for storage and later distributed to the industrial customers by road. Finished consumer products containing the notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale. The notified chemical will also be imported as a component in finished consumer products.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products. The proposed usage concentration of the notified chemical in various consumer products will be:

- ≤ 1% in deodorant, hand cream, and hairstyling (non-spray) products;
- ≤ 1.85% in fine fragrances;
- ≤ 2% in face cream, body lotion and other leave-on cosmetic products (such as makeup, makeup remover and eye products);
- ≤ 2.5% in hairspray and household cleaning products;
- ≤ 5% in rinse-off cosmetic products (such as hand soap, shampoo, shower gel and facial cleaners); and
- ≤ 10% in air-care products (such as candles and air-fresheners).

OPERATION DESCRIPTION
Reformulation
The procedures for reformulating fragrance oils containing the notified chemical will vary and will depend on the nature of the cosmetic and household products, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation process will be highly automated and occur in an enclosed system with adequate ventilation. This will be followed by automatic filling of the finished products into containers of various sizes which will be distributed to retail outlets. During the reformulation process, samples will be taken for quality control testing.

End-use
Household cleaning products
Finished household cleaning products containing the notified chemical (at ≤ 2.5% concentration) will be used by the general public and professional cleaners. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines or open processes, and manually applied by sponge, mop, spray or brush followed by wiping or rinsing.

Cosmetics
The finished cosmetic products containing the notified chemical (at ≤ 5% concentration) will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

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	Unknown	Incidental exposure only
Plant operators-mixing/compounding	4	250
Plant operators-drum handling	1	250
Plant operators-drum cleaning/washing	2	250
Plant operators-equipment cleaning/washing	2	250
Plant operators-quality control	1	250
Professional users- (e.g. hairdressers, cleaners, etc.)	8	250

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemical at ≤ 10% concentration in fragrance oils and end-use products, only in the event of an unlikely accidental rupture of containers. If such an event occurs, workers may be exposed through dermal, ocular or perhaps inhalation exposure. Exposure should be minimised through the stated use by the notifier of personal protective equipment (PPE) including protective coveralls, impervious gloves and eye protection.

Reformulation

Reformulation is expected to highly automated and occur in an enclosed system with adequate ventilation, therefore limited exposure is expected. However, workers may be exposed to the notified chemical at ≤ 10% concentration via dermal, ocular and inhalation routes during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure should be minimised through the stated use by the notifier of PPE including protective clothing, eye protection, impervious gloves and respiratory protection (as appropriate).

End-use

Exposure to the notified chemical in end-use products (at ≤ 5% concentration) may occur in professions where the services provided involve the application of cosmetics 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 may use appropriate PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 5% concentration) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure (e.g. through the use of spray products) are also possible.

Data on typical use patterns of cosmetic and household product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2010; Cadby et al., 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) of 100% was assumed for the notified chemical for calculation purposes. 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%. 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)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	2.0	1	2.4438
Face cream	1540	2.0	1	0.4813
Hand cream	2160	1.0	1	0.3375
Fine fragrances	750	1.85	1	0.2168
Deodorant spray	1430	1.0	1	0.2344
Shampoo	10460	5.0	0.01	0.0817
Conditioner	3920	5.0	0.01	0.0306
Shower gel	18670	5.0	0.01	0.1459
Hand soap	20000	5.0	0.01	0.1563
Hair styling products	4000	1.0	0.1	0.0625
Total				**4.1906**

C = maximum intended concentration of notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

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

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	2.5	0.95	10	0.0854
Fabric softener	90	2.5	0.95	10	0.0334
Total					**0.1188**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	2.5	1980	0.01	0.01	0.007	0.0008
Dishwashing liquid	3	2.5	1980	0.0093	0.01	0.03	0.0063
All-purpose cleaner	1	2.5	1980	1	0.01	0.007	0.0541
Total							**0.0612**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

Hairspray (Inhalation exposure):

Product type	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration zone 1 (min)	Exposure duration zone 2 (min)	Fraction inhaled (%)	Volume zone 1 (m^3)	Volume zone 2 (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	20	2.5	20	15	20	50	1	10	**0.0805**

C = maximum intended concentration of notified chemical
Total daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × 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 at the maximum intended concentrations as specified by the notifier in various product types. This would result in a combined internal dose of 4.451 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 cleaning 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 > 5.05 mg/L/4 hour; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (20%)	no evidence of sensitisation
Rat, repeat dose oral gavage toxicity – 29 days for males and 40-53 days for females.	NOAEL (parental) = 500 mg/kg bw/day NOAEL (reprod/develop) = 500 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration	non genotoxic

Toxicokinetics

Based on the low molecular weight (156.27 Da) of the notified chemical absorption across biological membranes may occur.

Acute toxicity

The notified chemical is of low acute toxicity via the oral, dermal and inhalation routes.

Irritation and sensitisation

Based on studies conducted in rabbits, the notified chemical is considered to be slightly irritating to the skin and eyes.

Sensitisation

The notified chemical was determined to be a skin sensitiser in a mouse local lymph node assay (LLNA) with stimulation indices of 2.28, 4.43 and 4.47 at 25%, 50% and 100%, respectively. The EC_3 value was calculated to be 33.4%. The sensitising potential of the notified chemical was also tested in a separate human repeat insult patch test (HRIPT). The notified chemical was not a skin sensitizer when tested at 20% concentration (with 106 subjects completing the study).

Repeated dose toxicity

In a combined oral repeated dose toxicity study with reproduction/developmental screening in rats, the notified chemical was administered daily by gavage for 29 days for males and for 40-53 days for females. The dose levels were 50, 150 and 500 mg/kg bw/day. Treatment related effects were observed in the thyroid gland, liver, kidneys, and adrenal glands; however, the effects were not considered to be adverse or relevant to humans.

No reproduction or developmental toxicity was observed up to the highest dose tested.

The No Observed Adverse Effect Level (NOAEL) for paternal and reproduction/developmental toxicity was therefore established as 500 mg/kg bw/day in this study.

Mutagenicity/Genotoxicity

The notified chemical tested negative in a bacterial reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli* strains and negative in an *in vitro* mammalian chromosome aberration assay 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*
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided, the critical health effect of the notified chemical is as a skin sensitiser. It is also slightly irritating to the skin and eyes.

Reformulation
During reformulation, workers may be exposed to the notified chemical at ≤ 10% concentration. At the low proposed use concentration irritation effects are not expected, however workers may be at risk of sensitisation. It is anticipated that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit worker exposure. Therefore, provided that control measures are in place to minimise worker exposure, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers and beauty salon workers), or the use of household products in the cleaning industry, may be exposed to the notified chemical at ≤ 5% concentration. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various products containing the notified chemical.

6.3.2. Public Health
Cosmetic and household products containing the notified chemical will be available to the public. The main route of exposure is expected to be dermal, with some potential for accidental ocular or inhalation exposure.

Irritation
The notified chemical is slightly irritating to skin and eyes. However, irritation effects are not expected from use of the notified chemical at the proposed low concentrations (≤ 5%) in cosmetic and household cleaning products.

Sensitisation
An animal sensitisation study (LLNA) and a human sensitisation study were provided for the notified chemical and based on the results of the LLNA study the notified chemical is considered as a sensitiser with an EC_3 value of 33.4%. When tested at 20% concentration in a human repeat insult patch study, the notified chemical was not a skin sensitiser.

Proposed methods for the quantitative risk assessment of the dermal sensitisation have been the subject of significant discussion (i.e., Api *et al.,* 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in cosmetic and household products may be estimated (SCCS, 2012 and Cadby *et al*, 2002). Consideration of each of the skin sensitisation studies conducted on the notified chemical and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 70.64 µg/cm^2/day. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 100.

Product type	Proposed usage concentration (%)	CEL ($\mu g/cm^2$)	AEL ($\mu g/cm^2$)
Fine fragrances	1.85	69.38	70.64
Other leave-on cosmetics (assumed: face cream)	2	54.51	70.64
Rinse-off cosmetics (assumed: hand wash soap)	5	11.63	70.64
Household product (assumed: cleaning liquid)	2.5	1.16	70.64

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at ≤ 1.85% concentration in fine fragrances, ≤ 2% concentration in other leave-on cosmetic products (using face cream as a worst case example), at ≤ 5% concentration in rinse-off cosmetic products (using hand wash soap as a worst case example) and at ≤ 2.5% concentration in household products (using cleaning liquid as a worst case example) is not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Repeated dose toxicity
The repeated dose toxicity potential of the notified chemical was estimated by calculation of the margin of exposure (MOE) using the worst case exposure scenario from use of multiple products of 4.451 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 500 mg/kg bw/day, which was established in the combined repeated dose oral toxicity study with the reproduction/developmental toxicity screening test performed on the notified chemical. The margin of exposure (MOE) was estimated to be 112 for a person using daily all types of products containing the notified chemical. A MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the available information, the risk to the public associated with the use of the notified chemical at ≤ 1% in deodorant, hand cream, and hairstyling (non-spray) products; ≤ 1.85% in fine fragrances, ≤ 2% in other leave-on cosmetic products, ≤ 2.5% in hairspray and household cleaning products; ≤ 5% in rinse-off cosmetic products or ≤ 10% in air-care products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance oil formulations for local reformulation into finished 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 chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

The fragrance oil formulations containing the notified chemical will be blended with other ingredients in the manufacture of cosmetic 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 through licensed waste management facility.

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 across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL
It is expected that some of the product containing the notified chemical will remain in end-use containers. 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 Australia, the majority of the notified chemical is expected to be released to sewers on a nationwide basis. The submitted biodegradation study indicates that the notified chemical is not readily biodegradable (2% in 28 days). For the details of the environmental fate study please refer to Appendix C.

The half-life of the notified chemical in air is calculated to be 3.72 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 STPs the notified chemical is expected to be efficiently removed (based on its low water solubility and high partition coefficient) from effluent by adsorption to sludge or via volatilization pathways (based on high vapour pressure). Therefore, only a small portion of the notified chemical may be released to surface waters. 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 low mobility based on its soil adsorption coefficient (Log K_{OC} =2.87-3.12). The notified chemical has the potential to bioaccumulate based on its high n-octanol-water partition coefficient value (log P_{OW}=3.97-5.24) and lack of ready biodegradability. However, the notified chemical is not expected to be significantly released to surface waters. 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)

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	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 18.7 µg/kg and 37.5 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 = 3.35 mg/L	Toxic to fish
Daphnia Toxicity (48 h)	EC50 = 3.2 mg/L	Toxic to aquatic invertebrates
Algal Toxicity (72 h)	EC50 = 6 mg/L NOEC = 1.8 mg/L	Toxic to algae

Based on the acute ecotoxicological endpoints, the notified chemical is expected to be toxic to aquatic life. Therefore, the notified chemical is classified as "Acute Category 2: Toxic to aquatic life" according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations 2009). On the basis of acute toxicity data, NOEC value and lack of biodegradability, 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)	1.80 mg/L
Assessment Factor	100
Mitigation Factor	1.00
PNEC:	18.00 µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.56	18	0.031
Q – Ocean	0.06	18	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. On the basis of the PEC/PNEC ratio and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -20 °C

Method	OECD TG 102 Freezing Point.
Remarks	Dry ice/acetone bath method
Test Facility	Envigo (2016a)

Boiling Point 174 °C at 102.7 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Determined by using differential scanning calorimetry
Test Facility	Envigo (2016a)

Density 846 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Pycnometer method
Test Facility	Envigo (2016a)

Vapour Pressure 0.342 kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Isoteniscope method
Test Facility	Envigo (2016b)

Water Solubility 7.09 x 10^{-3} 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	Envigo (2016a)

Partition Coefficient (n-octanol/water) log Pow = 4.67 and 5.24

Method	OECD TG 117 Partition Coefficient (n-octanol/water) EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	High Performance Liquid Chromatography (HPLC) method. The capacity factor was calculated for each test item peak and the partition coefficient was determined with reference to the calibration curve.
Test Facility	Envigo (2016a)

Partition Coefficient (n-octanol/water) log Pow = 3.97 at 25 °C

Method	OECD TG 123 Partition Coefficient (n-octanol/water): Slow-Stirring Method
Remarks	Slow-Stirring Method
Test Facility	Envigo (2017a)

Surface Tension 70.3 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions.
Remarks	Concentration: 90% saturated solutions of test item in water
Test Facility	Envigo (2016a)

Adsorption/Desorption log K_{oc} = 2.87 and 3.12

Method	OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage

	Sludge Using HPLC
Remarks	High Performance Liquid Chromatography (HPLC) method. The retention times, capacity factors and the adsorption coefficients (K_{oc}) were determined for two peaks.
Test Facility	Envigo (2016c)

Flash Point 47 ± 2 °C at 100.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method
Test Facility	Envigo (2016d)

Autoignition Temperature 194 ± 5 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	Carbolite flash heater method
Test Facility	Envigo (2016d)

Explosive Properties Negative

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 (2016d)

Oxidizing Properties Negative

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks	No structural alerts within the chemical structure of the test item.
Test Facility	Envigo (2016d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Wistar
Vehicle	Arachis oil BP (for 300 mg/kg bw) Nil (for 2,000 mg/kg bw)
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	One animal exposed to high dose showed hunched posture 4 hours after exposure.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	No unscheduled mortalities occurred during study. All animals showed expected gains in bodyweight over the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Envigo (2016e)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 402 Acute Dermal Toxicity.
Species/Strain	Rat/Wistar
Vehicle	Nil
Type of dressing	Semi-occlusive
Remarks - Method	No protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No signs of local toxicity were noted.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted during necroscopy.
Remarks - Results	All treated animals showed expected body weight gain during the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	Envigo (2016f)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 403 Acute Inhalation Toxicity.
Species/Strain	Rat/Wistar
Vehicle	Nil
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	Aerosol
Particle Size	4.98 μm
Remarks - Method	An MMAD of 4.98 μm was obtained and this was higher than the range specified (1-4 μm) in the test guideline. The geometric standard deviation (GSD) was also higher (5.47) than the accepted range of 1.5-3.0. The study authors asserted that these deviations are probably due to the low levels of non-volatile substances in the test material.

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	5/sex	6.43	5.05	0/10

LC50	> 5.05 mg/L/4 hours
Signs of Toxicity	All animals showed hunched posture and pilo-erection immediately after removal from the exposure chamber and these symptoms persisted up to day 1 of observation. Wet fur on all animals was observed during exposure and up to 1 hour after exposure. The study authors indicated that these effects were probably due to the restraining procedure during exposure. Decreased respiration rate was observed in all animals during exposure. Immediately after exposure, all animals showed increased respiration rate and this persisted up to day 1 of observation. Ataxia and red or brown staining around the nose and mouth were also observed and these symptoms persisted up to 1 hour. On day 2, all animals showed increased respiration, hunched posture and pilo-erection. No treatment related abnormalities were observed after day 2.
Effects in Organs	No abnormalities were detected at necropsy.
Remarks - Results	On day 1 of observation, 3 males and 2 females showed body weight reduction. On day 3 and 14 of observation, 3 females and 2 females, respectively, showed body weight reduction. No unscheduled mortality occurred during the study.
CONCLUSION	The notified chemical is of low acute toxicity via inhalation.
TEST FACILITY	Envigo (2017b)

B.4. Irritation – skin

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White (Hsdlf:NZW)

Number of Animals	2 M
Vehicle	Nil
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Erythema/Eschar	2	2	2	< 14 days	0
Oedema	2	2	2	< 14 days	0

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

Remarks - Results	No mortality or signs of systemic toxicity were noted. Slight to well-defined erythema was noted in both animals immediately after patch removal and persisted at the 1-hour observation. Well-defined erythema was noted in both animals at the 24-hour observation and persisted up to day 7 observation. Loss of skin elasticity was noted on the treated sites on both animals at the 72 hour observation. On days 7 and 14 observations, crust formation and slight desquamation, respectively, was observed on the treated sites on both animals. Slight oedema was noted in both animals immediately after patch removal and persisted up to day 7 observation. Changes in body weight gain were within the range expected for rats used in this type of study.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Envigo (2016g)

B.5. Irritation – eye

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White (Hsdlf:NZW)
Number of Animals	2 M
Vehicle	Nil
Observation Period	7 days
Remarks - Method	Initial eye reaction following application of the test item was not recorded for one animal. No significant 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	1	1.33	2.0	< 7 days	0
Conjunctiva: chemosis	0.66	0.66	2.0	< 72 h	0
Conjunctiva: discharge	0.0	0.66	1.0	< 72 h	0
Corneal opacity	0.0	0.0	0.0	-	0
Iridial inflammation	0.0	0.0	0.0	-	0

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

Remarks - Results	Moderate reddening of the conjunctivae was noted in both animals at the 1-hour observation and slight reddening persisted up to the 48-hour observation in one animal and up to the 72-hour observation in the other animal. Moderate to slight chemosis was observed in both animals at the 1-hour observation and persisted in one animal at the 48-hour observation. Slight ocular discharge noted in both animals at the 1-hour observation and persisted in one animal at the 48-hour observation. All signs of irritation were resolved at the 7-day observation. No abnormal body weight changes were observed during the study. There was no unscheduled mortality or clinical signs of systemic toxicity
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Envigo (2016h)

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

TEST SUBSTANCE	Notified chemical (98.3% purity)
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil (4:1)
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde. Conducted in parallel with the test substance.
Remarks - Method	A preliminary study was conducted using the test substance at concentrations up to 100%. Variation in ear thickness during the observation period was less than 25% from day 1 at all concentrations. Based on the results of the preliminary study, the highest concentration selected for the main study was 100%.

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	1016.23	-
25	5 F	2316.85	2.28
50	5 F	4501.15	4.43
100	5 F	4539.12	4.47
Positive Control			
25	5 F	5372.34	5.29

EC3	33.4%
Remarks - Results	No unscheduled mortalities or signs of systemic toxicity were observed during study period. The stimulation index was > 3 in the 50% and 100% test group, indicating a sensitising response. The stimulation index (EC_3) was calculated to be 33.4%. The positive control behaved as expected, confirming the validity of the test system.

CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Envigo (2016i)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (5% and 20%)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.15 mL test substance (5% or 20%) were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications during the induction period. Patches were removed by the subjects after 24 hours and graded by technicians after an additional 24 hours (or 48 hours for patches applied on Friday). Rest Period: 10-21 days Challenge Procedure: Patches were applied to a naïve site. Patches were removed by a technician after 24 hours and test sites were evaluated. Sites were re-evaluated at 48 and 72 hours post-patch removal.
Study Group	85 F, 29 M; age range 18-70 years
Vehicle	Ethanol:diethyl phthalate (1:3)
Remarks - Method	The test substance was applied on a 3.63 cm^2 occlusive patch.
RESULTS	
Remarks - Results	106/114 subjects completed the study. Eights subjects discontinued with the study for reasons unrelated to the test substance. Two subjects did not attend the 48 hour evaluation but attended the 72 hour and 96 hour evaluations and four subjects did not attend the 72 hour evaluation but attended the 96 hour evaluation. No adverse responses were noted at induction and challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories (2017)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (97.7% purity)
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rats/Crl:WI (Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 29 days for males (2 weeks prior to mating, during mating and up to the day prior to scheduled necropsy) and 40-53 days for females (during 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation) Dose regimen: 7 days per week
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations. In a dose range finding study, 3 female rats were exposed to 500 and 1,000 mg/kg bw/day of the notified chemical for 10 days. Low weight gain, weight loss and slight increase in liver weights were observed for animals

treated with 1,000 mg/kg bw/day. Based on these results 0, 50, 150 and 500 mg/kg bw/day was chosen for the main study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10/sex	0	0/20
low dose	10/sex	50	0/20
mid dose	10/sex	150	0/20
high dose	10/sex	500	0/20

Mortality and Time to Death

No unscheduled mortality occurred during the study period.

Clinical Observations

No treatment-related clinical signs of toxicological relevance were noted throughout the treatment and recovery periods.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Statistically significant changes in clinical biochemistry parameters consisted of:

- higher total protein in males treated with low, mid and high doses;
- higher creatinine and calcium levels in males treated with high dose; and
- higher chloride levels in females treated with high dose.

The study authors considered these changes as not toxicologically relevant as they were within the range considered normal for rats of this age and strain and no apparent relation to morphological lesions was observed.

Effects in Organs

Treatment related effects were observed in the thyroid gland, liver, kidneys, and adrenal glands.

- Slightly increased severity of hypertrophy of follicular cells in thyroid glands was observed for males treated with mid and high doses. The study authors regarded this effect to be an adaptive change and considered to be non-adverse at the incidences and severities recorded.
- Slight hepatocellular hypertrophy was observed in the liver for both sexes treated with mid and high doses. This was accompanied by higher liver weights in males treated with mid dose (approximately 17% higher), and both sexes (males approximately 32% higher and females approximately 15% higher) treated with high doses. These findings occurred without any degenerative histopathological changes or corroborative changes in clinical biochemistry parameters and were therefore considered by the study authors to be adaptive and non-adverse in nature.
- Males treated with all doses showed increased incidence of severity of hyaline droplet accumulation in kidneys which was accompanied by slightly increased severity of tubular basophilia at high dose and granular casts in one male at low dose and two males at high dose. These findings of the kidney in male animals were considered by the study authors to be directly linked to the accumulation of alpha 2μ-globulin, which is unique to the male rat and therefore to be of no relevance to humans.
- Females treated with high dose showed increased incidence and severity of vacuolation of the zona glomerulosa in adrenal glands. The study authors indicated that given the slight nature of vacuolation of the zona glomerulosa of the adrenal glands, and absence of any degenerative findings, this effect was considered to be non-adverse. In addition, males treated with mid and high doses showed statistically significant higher adrenal gland weights. In the absence of morphological evidence, the study authors considered the higher adrenalin gland weight to be non-adverse in nature.

Reproductive/developmental findings

No treatment related changes were noted in any of the reproductive and developmental parameters investigated in this study.

Remarks – Results

Treatment related effects were observed in the thyroid gland, liver, kidneys, and adrenal glands; however, the effects were not considered to be adverse or relevant to humans.

No reproduction or developmental toxicity was observed up to the highest dose tested (500 mg/kg bw/day).

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) for parental and reproduction/developmental toxicity was established as 500 mg/kg bw/day in this study, based on absence of test substance related adverse effects at all doses tested.

TEST FACILITY Charles River Laboratories (2016)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (98.3% purity)

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure

Species/Strain *Salmonella typhimurium*: TA1535, TA1537, TA98 and TA100
Escherichia coli: WP2uvrA

Metabolic Activation System Aroclor induced induced rat liver (S9 homogenate)

Concentration Range in Main Test
Test 1
a) With metabolic activation: 10, 33, 100, 333, 1,000, and 3,330 µg/plate
b) Without metabolic activation: 10, 33, 100, 333, and 1,000 µg/plate

Test 2
a) With metabolic activation: 10, 33, 100, 333, 1,000, and 3,330 µg/plate
b) Without metabolic activation: 10, 33, 100, 333, and 1,000 µg/plate

Test 3 (TA 1537 only)
a) With metabolic activation: 100, 333, 1,000, 3,330 and 5,000 µg/plate

Vehicle Ethanol

Remarks - Method A dose-finding study (3 - 5,000 µg/plate) was performed to determine the toxicity of the test material (on TA100 and WP2uvrA only).

Vehicle and positive controls were used in parallel with the test material.

Positive controls used were:
i) without S9: sodium azide (TA1535), 6-chloro-9-(3-propylamino)-2-methoxyacridine dihydrochloride or ICR 191 (TA1537), 2-nitrofluorene (TA98), methylmethanesulfonate (TA100) and 4-nitroquinoline N-oxide (WP2uvrA);
ii) with S9: 2-aminoanthracene.

As no toxicity and no precipitate was observed in Test 2 with metabolic activation with tester strain TA 1537, an additional mutation test was performed on this strain only with metabolic activation at doses up to 5,000 µg/plate.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 333	≥ 100	> 1,000	Negative
Test 2		≥ 333	> 1,000	Negative
Present				
Test 1	≥ 1,000	≥ 1,000	≥ 3,330*	Negative

Test 2	≥ 1,000	≥ 3,330*	Negative
Test 3	≥ 5,000	≥ 3,330*	Negative

*Precipitation was observed at the start of the incubation period but no precipitate was observed at the end of the incubation period

Remarks - Results

In the preliminary toxicity study, the test material was toxic to the TA100 strain at ≥ 333 µg/plate without metabolic activation and at ≥ 1,000 µg/plate with metabolic activation.

In the main studies, the test substance caused a visible reduction in the growth of the bacterial background lawn to all strains, from 1,000 and 333 µg/plate, with and without metabolic activation, respectively.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains up to and including the maximum dose, either with or without metabolic activation.

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

CONCLUSION

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

TEST FACILITY

WIL Research (2014a)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical (98.3% purity)

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Human

Cell Type/Cell Line: Lymphocytes

Metabolic Activation System: S9 mix from phenobarbital and β-naphthoflavone induced rat liver

Vehicle: Ethanol

Remarks - Method:
Negative control: ethanol
Positive control:
without metabolic activation – Mitomycin C
with metabolic activation - Cyclophosphamide

A dose-finding study (10-1,562 µg/plate without and 10-1,000 with metabolic activation) was performed to determine the toxicity of the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	30*, 50, 70*, 100, 130* and 160	3 h	24 h
Test 2a	30*, 50, 70*, 100*, 130, 160 and 230	24 h	24 h
Test 2b	30*, 50, 70*, 100*, 130, 160 and 230	48 h	48 h
Present			
Test 1	50*, 100*, 130*, 160, 200, 230, 260 and 300	3 h	24 h
Test 2	30*, 50, 70, 100*, 130, 160* and 230	3 h	48 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test**	*Precipitation*	*Genotoxic Effect*

Absent				
Test 1	≥ 333	≥ 160	> 160	Negative
Test 2	≥ 333	≥ 130	> 230	Negative
Test 3	≥ 333	≥ 100	> 230	Negative
Present				
Test 1	≥ 333	≥ 160	> 300	Negative
Test 2	-	≥ 160	> 230	Negative

* > 50% inhibition of mitotic index

Remarks - Results	Both in the absence and presence of metabolic activation, the test substance did not induce a statistically significant or biologically relevant increase in the number of cells with chromosome aberrations. There were also no effects on the number of polyploid cells and cells with endoreduplicated chromosomes, with or without metabolic activation. The positive controls behaved as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	WIL Research (2014b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310 Ready Biodegradability: CO_2 in sealed vessels (Headspace Test).
Inoculum	Activated Sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Inorganic Carbon (ThIC) (CO_2 production in the vessels was determined by measuring the increase in the concentration of inorganic carbon (IC) in the headspace)
Remarks - Method	An aliquot of test item was injected through the septum of each vessel to give the required concentration of 26.0 mg/L equivalent to 20 mg C/L.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	0	0	1
14	1	8	37
21	1	14	42
28	2		

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 77% within 14 days indicating the suitability of the inoculums. The toxicity control attained 42% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The test substance attained 2% biodegradation after 28 days.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Envigo (2016j)

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	*Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	Acetone
Water Hardness	130 mg $CaCO_3$/L
Analytical Monitoring	Chromatography and mass spectrometry
Remarks – Method	The test substance was weighed and dissolved into acetone with volume made up to 5 ml to prepare the stock solution of 80 mg/ml. The stock solution was used to make further dilutions.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	0	7	0	0	0	0	0
Control solvent	0	7	0	0	0	0	0

3.8	1.93	7	0	0	0	0	0
4.6	2.34	7	0	0	0	14.3	14.3
5.5	2.70	7	0	0	0	0	14.3
6.6	3.35	7	0	0	28.6	28.6	28.6
7.9	4.45	7	0	28.6	71.4	100.0	100.0

LC50	3.35 mg/L at 96 hours.
NOEC	Not determined
Remarks – Results	All validity criteria for the test were satisfied, except the deviation of measured concentrations from the nominal concentrations was greater than 20% and the results were calculated based on the measured concentrations (geometric mean). The loss could be attributed to the volatilization or due to the adsorption to the fish body surface. The test fish showed the sign of visible abnormalities of rollover, imbalance, diminished swimming capacity, abnormal breathing, and abnormal static in the treated groups.
CONCLUSION	The notified chemical is toxic to fish
TEST FACILITY	Suzhou Xishan Zhongke Drug R&D Co., Ltd. (2015)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks - Method	The test item solutions were prepared by stirring an excess (100 mg/L) of test item in water for 24 hours. The solution was filtered to produce a 100% v/v saturated solution. The saturated solution was used to prepare further dilutions.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised Daphnia (%)*	
Nominal (% v/v saturated solution)	*Actual (the geometric mean measured concentrations)*		*24 h*	*48 h*
Control	0	20	0	0
10	1.77	20	0	15
18	1.97	20	0	5
32	5.63	20	0	90
56	11.1	20	25	100
100	22.7	20	100	100

EC50	3.2 mg/L (2.7-4.0) at 48 hours
NOEC	2.0 mg/L at 48 hours
Remarks - Results	All validity criteria were met. The results from the positive control with potassium dichromate were within the normal range for this reference item. Sub-lethal effects of exposure were observed in the 10, 18 and 32 mg/L test concentrations.
CONCLUSION	The notified chemical is toxic to aquatic invertebrates
TEST FACILITY	Envigo (2016k)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0, 3.2, 10, 32 and 100% v/v saturated solution Actual: 0.14, 0.43, 1.8, 5.1 and 20 mg/L
Auxiliary Solvent	None
Water Hardness	Not determined
Analytical Monitoring	Gas Chromatography
Remarks - Method	The test item solutions were prepared by stirring an excess (100 mg/L) of test item in water for 24 hours. The solution was filtered to produce a 100% v/v saturated solution. The saturated solution was used to prepare further dilutions. Due to the potentially volatile nature of the test item, testing was conducted in completely filled stoppered test vessels in order to minimize possible losses due to volatilization. Additional sodium bicarbonate was added to the culture medium to provide a source of carbon dioxide for algal growth.

RESULTS

Biomass		*Growth*	
EC50 *mg/L at 72 h*	*NOEC* *mg/L*	*EC50* *mg/L at 72 h*	*NOEC* *mg/L*
3.8	1.8	6.0	1.8

Remarks - Results	All validity criteria were met. The results are based on the geometric mean measured test concentrations.
CONCLUSION	The notified chemical is toxic to algae
TEST FACILITY	Envigo (2016l)

BIBLIOGRAPHY

ACI (2010) Consumer Product Ingredient Safety, Exposure and risk screening methods for consumer product ingredients, 2nd Edition, American Cleaning Institute, Washington DC.

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA and Safford R (2008) Dermal Sensitisation Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Regulatory Toxicology and Pharmacology, 52:3-23.

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

Charles River Laboratories (2016) Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental toxicity Screening Test of IFF 05-0293 in Rats by Oral Gavage. (Study No: 507918) New Jersey USA (Unpublished report submitted by the notifier).

Clinical Research Laboratories (2017) Repeat Insult Patch Test (RIPT) – Shelanski Method (Study No: CRL2017-0250, April, 2017). Piscataway, New Jersey, Clinical Research Laboratories, LLC (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

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 (2016a) FRET 05-0293: Determination of General Physico-Chemical Properties (Study No: MG75XX, June, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016b) FRET 05-0293: Determination of Vapour Pressure (Study No: SY10JD, August, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016c) FRET 05-0293: Determination of Adsorption Coefficient (Study No: GD79KJ, June, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016d) FRET 05-0293: Determination of Hazardous Physico-Chemical Properties (Study No: WG82SD, August, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016e) FRET 05-0293: Acute Oral Toxicity in the Rat – Acute Toxic Class Method (Study No: RG57QN, October, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016f) FRET 05-0293: Acute Dermal Toxicity (Limit Test) in the Rat (Study No: KH38KL, November, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016g) FRET 05-0293: Acute Dermal Irritation in the Rabbit (Study No: CT69VP, October, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016h) FRET 05-0293: Acute Eye Irritation in the Rabbit (Study No: BH52QH, August, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016i) FRET 05-0293: Local Lymph Node Assay in the Mouse – Individual Method (Study No: RS31JP, October, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016j) FRET 05-0293: Assessment of Ready Biodegradability; CO_2 in Sealed Vessels (CO_2 Headspace Test) (Study No: RR62VY, September, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016k) FRET 05-0293: Daphnia sp., 48-Hour Acute Immobilization Test (Study No: SL82GL, September, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2016l) FRET 05-0293: Algal Growth Inhibition Test (Study No: FF69QW, October, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017a) FRET 05-0293: Determination of Partition Coefficient (n-Octanol/Water) (Study No: SJ22NY, February, 2017). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Envigo (2017b) FRET 05-0293: Acute Inhalation Toxicity (Nose Only) Study in the Rat (Study No: YV67YJ, February, 2017). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

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. (2006) Exposure data for personal care products : Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant, Food and Chemcial Toxicology 44 (2006) 2008-2018.

RIVM (2010) Observations on the Methodology for Quantitative Risk Assessment of Dermal Allergens, Report 320015003/2010, National Institute for Public Health and the Environment.

Rothe, H., Fautz, R., Gerber, E., Neumann, L., Rettinger, K., Schuh, W., Gronewold, C (2006) Special aspects of cosmetic spray evaluations: Principles on inhalation risk assessment, Toxicology Letters 205 (2011) 97-104.

SCCS (2012) The SCCS' 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. Principle considerations for the risk assessment of sprayed consumer products, Toxicology Letters 227 (2014) 41-49.

Suzhou Xishan Zhongke Drug R&D Co., Ltd. (2016) Fish, Acute Toxicity Test for FRET 05-0293 (Study No: 2015-152-01-01, January, 2016). Suzhou City, Jiangsu Province, China, Suzhou Xishan Zhongke Drug R&D Co., Ltd (Unpublished report submitted by the notifier).

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

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 Research (2014a) Evaluation of the Mutagenic Activity of IFF 05-0293 in the Salmonella typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay (with Independent Repeat) (Study No: 504728, June, 2014). Hertogenbosch, The Netherlands, WIL Research Europe B.V. (Unpublished report submitted by the notifier).

WIL Research (2014b) Evaluation of the Ability of IFF 05-0293 to Induce Chromosome Aberration in Cultured Peripheral Human Lymphocytes (with Repeat Experiment) (Study No: 504730, July, 2014). Hertogenbosch, The Netherlands, WIL Research Europe B.V. (Unpublished report submitted by the notifier).