File No: LTD/2016

June 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

6-Octen-1-ol, 2,4,7-trimethyl-

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/2016	Givaudan Singapore Pte Ltd	6-Octen-1-ol, 2,4,7-trimethyl-	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*
Skin Corrosion/Irritation (Category 2)	H315 – Causes skin irritation
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

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 Corrosion/Irritation (Category 2): H315 – Causes skin irritation
  - 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.

Safety Data Sheet

- The SDS provided by the notifier should be amended as follows:
  - Skin Corrosion/Irritation (Category 2): H315 – Causes skin irritation
  - Skin Sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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

- 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 skin and eye contact

- 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:
  - Impervious gloves
  - Protective goggles
  - Coveralls

  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 is intended to exceed 1% in fine fragrances, 0.25% in other cosmetic products, 1% in fabric care products or 0.1% in other household 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(S)
Givaudan Singapore Pte Ltd (ABN: 79 368 011 578)
1 Pioneer Turn
SINGAPORE 627576

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)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China (2017)
EU (2017)
Philippines (2017)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Pomelol

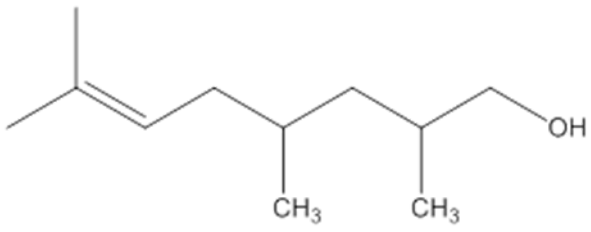
CAS NUMBER
1913285-57-0

CHEMICAL NAME
6-Octen-1-ol, 2,4,7-trimethyl-

OTHER NAME
GR-50-3010

MOLECULAR FORMULA
$C_{11}H_{22}O$

STRUCTURAL FORMULA



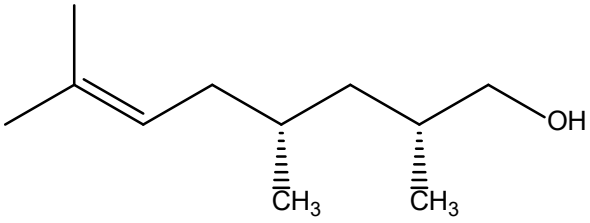
MOLECULAR WEIGHT
170.29 g/mol

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

3. COMPOSITION

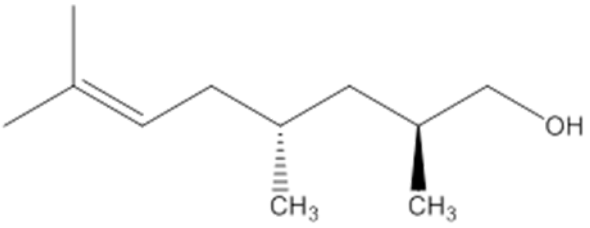
DEGREE OF PURITY
> 94%

The notified chemical is a mixture of four stereoisomers (2 diastereoisomers and 2 enantiomers). The diastereoisomers are in roughly equimolar proportions of 42.8% and 51.5%. The identity of the major and minor diastereoisomer has not been specified.



+ Enantiomer

Chemical Name: 6-Octen-1-ol, 2,4,7-trimethyl-, (2*R*,4*R*)-*rel*-
CAS number: 2073819-63-1



+ Enantiomer

Chemical Name: 6-Octen-1-ol, 2,4,7-trimethyl-, (2*R*,4*S*)-*rel*-
CAS number: 2073819-84-6

IMPURITIES (> 1% BY WEIGHT)

Chemical Name	3,6-Octadien-1-ol, 2,4,7-trimethyl-, (2Z)-		
CAS No.	Not assigned	*Weight %*	1.1
Chemical Name	3,6-Octadien-1-ol, 2,4,7-trimethyl-, (2E)-		
CAS No.	Not assigned	*Weight %*	2.2

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless to light yellow liquid

Property	Value	Data Source/Justification
Freezing Point	< -50 °C	Measured
Boiling Point	241 °C at 101.3 kPa	Measured
Density	856 kg/m^3 at 20 °C	Measured
Vapour Pressure	1 × 10^{-3} kPa at 20 °C	Measured
Water Solubility	0.101 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	No hydrolysable functionalities. Expected to be stable at environmental pH of 4-9
Partition Coefficient (n-octanol/water)	log Pow = 3.1 and 3.4 at 35 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.9 and 3.2 at 35 °C	Measured

Dissociation Constant	Not determined	No dissociable functionality
Surface Tension	40.8 mN/m	Measured
Flash Point	108 °C at 101.3 kPa	Measured
Flammability	Combustible liquid*	Based on measured flash point
Flammability in contact with water	Not highly flammable	Expert statement based on chemical structure
Autoignition Temperature	250 ± 10 °C	Measured
Explosive Properties	Not explosive	Expert statement based on chemical structure
Oxidising Properties	Not oxidising	Expert statement based on chemical structure

* Based on *Australian Standard AS1940*

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

The notified chemical has a flash point of 108 °C. Based on *Australian Standard AS1940* definitions for combustible liquids, a liquid that has a flash point of 150 °C or less is a Class C1 combustible liquid.

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 fragrance mixtures at ≤ 20% concentration for 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
Sydney and Perth

IDENTITY OF RECIPIENTS
Givaudan Pty Ltd

TRANSPORTATION AND PACKAGING
Fragrance mixtures containing the notified chemical at ≤ 20% concentration will be introduced by sea and air. The mixtures will be packaged in glass, lacquer-lined containers of sizes ranging from 1-190 kg.

Finished products containing the notified chemical at ≤ 1 % concentration will be packaged in containers suitable for retail sale.

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

Finished Consumer Product	*Max. Final Concentration of the Notified Chemical (%)*
Fine fragrance	1
Other cosmetic products	0.25
Household cleaning products	0.1
Fabric care	1

OPERATION DESCRIPTION

Reformulation
The procedures for reformulating the fragrance mixture containing the notified chemical at ≤ 20% concentration will likely vary depending on the nature of the cosmetic and household products, and may involve both automated and manual transfer steps. In general, it is expected that the reformulation processes will involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into consumer containers of various sizes.

End Use
Finished household cleaning products containing the notified chemical at ≤ 1 % concentration may be used by consumers and professional cleaners. The cleaning products will be generally applied with a cloth or sponge, mop or brush, or by spray followed by wiping. In some cases the cleaning product will be diluted with water prior to application.

The finished cosmetic products containing the notified chemical at ≤ 1 % 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	None	Incidental
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	4	2
Packaging	4	2
End users (professionals)	1 - 8	200

EXPOSURE DETAILS
Transport and storage
Transport, storage and warehouse workers may come into contact with the notified chemical at ≤ 20% concentration (in fragrance mixtures) or at ≤ 1 % concentration (in final formulated products), only in the event of accidental rupture of containers.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at ≤ 20% concentration may occur during handling of drums, during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of personal protective equipment (PPE) such as protective clothing, eye protection and impervious gloves.

End use professionals
Exposure to the notified chemical at ≤ 1 % concentration in end-use products may occur in professions where the services provided involve the application of cosmetic products to clients or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure are also

possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 1 % concentration) through the use of the cosmetic and household products. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables provided in various literatures (SCCS, 2012; 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) rate 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	0.25	1	0.3055
Face cream	1540	0.25	1	0.0602
Hand cream	2160	0.25	1	0.0844
Fine fragrances	750	1.00	1	0.1172
Deodorant (non-spray)	1500	0.25	1	0.0586
Shampoo	10460	0.25	0.01	0.0041
Conditioner	3920	0.25	0.01	0.0015
Shower gel	18670	0.25	0.01	0.0073
Hand wash soap	20000	0.25	0.01	0.0078
Hair styling products	4000	0.25	0.1	0.0156
Total				**0.6621**

C = maximum intended concentration of notified chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × Dermal Absorption) / Body Weight

Household products (indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (%)	Transfer (%)	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**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Amount × C × Product Retained × Transfer × Dermal Absorption) / Body Weight

Household products (direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	1.0	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	0.1	1980	0.009	0.01	0.03	0.0003
All-purpose cleaner	1	0.1	1980	1	0.01	0.007	0.0027
Total							**0.0027**

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

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	9.89	0.25	20	1	20	50	1	10	0.0080
Total									**0.0080**

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 0.7204 mg/kg bw/day.

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 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 low exposures (e.g. air fresheners and deodorants).

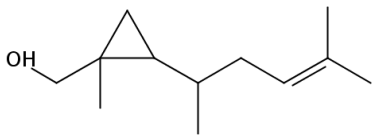
6.2. Human Health Effects Assessment

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 > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5.1 mg/L/4 hour; low toxicity
Skin irritation – *in vitro* (EpiSkin™ model)	irritating
Skin corrosion – *in vitro* (EpiDerm™ model)	non-corrosive
Eye irritation – *in vitro* Bovine Corneal Opacity Test (BCOP)	no prediction can be made
Skin sensitisation – *in chemico* Direct Peptide Reactivity Assay (DPRA)	no or minimal reactivity
Skin sensitisation – *in vitro* ARE-Nrf2 luciferase test	negative
Mouse, skin sensitisation – local lymph node assay (LLNA)*	evidence of sensitisation (EC3 = 62.5%)
Rat, repeat dose oral toxicity – 28 days*	NOAEL = 296 mg/kg bw/day (males); 300 mg/kg bw/day (females)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell micronucleus test	non genotoxic

*Test conducted on an analogue chemical (see below for details)

Analogue chemical



Analogue chemical (CAS No: 1655500-83-6)

The analogue chemical (Cyclopropanemethanol, 2-(1,4-dimethyl-3-penten-1-yl)-1-methyl-) is similar in structure to the notified chemical. It contains the same functionality, has a similar molecular weight and physicochemical properties (see Table below). Therefore the analogue chemical is considered acceptable to estimate the toxicity of the notified chemical.

	Notified chemical	Analogue chemical
Molecular weight	170.29 g/mol	182.3 g/mol
Water solubility	0.101 g/L at 20 °C	7×10^{-2} g/L at 20 °C
Partition coefficient (log Pow)	3.1 and 3.4 at 35 °C	3.5 at 35 °C

Toxicokinetics
Given the low molecular weight of the notified chemical (170.29 g/mol), absorption across the gastrointestinal and respiratory tract may occur. However, dermal absorption is expected to be limited given the low water solubility (0.101 g/L) and high lipophilicity (log Pow = 3.1 and 3.4) of the notified chemical, limiting penetration of the hydrophilic epidermis.

Acute toxicity
The notified chemical is of low acute oral and inhalation toxicity based on studies conducted in rats.

No acute dermal toxicity study was provided of the notified chemical.

Irritation and sensitisation
The notified chemical was found to be irritating but non-corrosive to the skin based on *in vitro* studies using reconstructed human epidermis models.

In an *in vitro* bovine corneal opacity and permeability (BCOP) test, the notified chemical caused an *in vitro* irritancy score (IVIS) of 11.4. Under the study guidelines, no prediction can be made for scores > 3 and ≤ 55. Further studies are therefore required to determine the eye irritation potential of the notified chemical.

One *in chemico* and one *in vitro* cell based assay were conducted to evaluate skin sensitisation potential of the notified chemical. The tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD, 2016). The tests are thus considered relevant for assessment of the skin sensitisation potential of test chemical, along with other supporting information.

The first key event in the AOP, commonly referred to as the molecular initiating event, for sensitisation is the covalent binding to nucleophilic centres in skin proteins. The *in chemico* Direct Peptide Reactivity Assay (DPRA) aims to address this key event by measuring the interaction of a test substance with cysteine and lysine-containing small synthetic peptides (representing the nucleophilic centres in skin protein).

The second key event in the AOP for sensitisation is the activation of keratinocytes which leads to upregulation of stress related proteins (cytokines) via transcriptional upregulation of the genes. The ARE-Nrf2 Luciferase Assay aims to address this key event by measuring the change in expression of luciferase gene under the transcriptional control of a constitutive promoter fused with an Antioxidant Response Element (ARE). The ARE is from a gene that is known to be upregulated by contact sensitisers.

The notified chemical showed a negative response in both AOP assays, suggesting the notified chemical may not be a skin sensitiser. However, according to the OECD test guideline, the DPRA assay does not encompass a metabolic system and therefore chemicals that require enzymatic bioactivation to exert their skin sensitisation potential (i.e. pro-haptens) may not be detected by the test method. Also chemicals that become sensitisers after abiotic transformation (i.e. auto-oxidation; pre-haptens) may not be detected. Similarly, the ARE-Nrf2 Luciferase Assay is reported to have limited metabolic capability, thus pro-haptens and pre-haptens (in particular with a slow oxidation rate) may also provide negative results.

QSAR analysis of the notified chemical suggests the notified chemical is a pre-hapten and predicted to be a weak skin sensitiser (OASIS TIMES Version 2.28). This is supported by the results of a mouse local lymph node assay (LLNA) on an analogue chemical which found the analogue chemical to be a weak skin sensitiser (EC3 = 62.5%).

Therefore, based on the results from the LLNA study on an analogue chemical in conjunction with QSAR analysis, the notified chemical is considered a category 1B skin sensitiser.

Repeated dose toxicity
No repeated dose toxicity studies were submitted for the notified chemical.

A repeated dose oral (diet) toxicity study on an analogue of the notified chemical was conducted in rats, in which the test substance was administered at 1,000 ppm (equivalent to 98 mg/kg bw/day for both sexes), 3,000 ppm (equivalent to 296 mg/kg bw/day for males and 300 mg/kg bw/day for females) and 10,000 ppm (equivalent to 1,011 mg/kg bw/day for males and 944 mg/kg bw/day for females) for 28 consecutive days, with a 14-day recovery period for high dose and control animals.

Test substance-related adverse effects observed in the kidneys of males after treatment at 10,000 ppm included tubular degeneration/regeneration, papillary cysts, cortical tubular dilation and hyperplasia pelvic urothelium. These adverse effects persisted at the end of the recovery period. Based on these effects, the No Observed (Adverse) Effect Level (NO(A)EL) for the analogue chemical was established as 3,000 ppm (equivalent to 296 mg/kg bw/day for males and 300 mg/kg bw/day for females).

Mutagenicity/Genotoxicity
The notified chemical tested negative in a bacterial reverse mutation assay and in an *in vitro* micronucleus test 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 Corrosion/Irritation (Category 2)	H315 – Causes skin irritation
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 available information, the notified chemical is a skin irritant and a weak skin sensitisier. The eye irritation potential of the notified chemical is not known.

Reformulation
During reformulation, workers may be at risk of skin and eye irritation when handling the notified chemical as introduced at ≤ 20% concentration. The notifier anticipates that worker exposure will be limited through the use of engineering controls such as enclosed systems, automated processes and local exhaust ventilation. The use of appropriate PPE (coveralls, imperious gloves and eye protection) will also be used to limit worker exposure.

End-Use
Workers involved in professions which involve professional cleaning or the application of cosmetic products containing the notified chemical to clients (*e.g.* beauty salon workers) may be exposed to the notified chemical at ≤ 1% concentration. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible. PPE may be employed by workers 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 for consumers using the various products containing the notified chemical.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health
Members of the public will experience widespread and frequent exposure to the notified chemical at ≤ 1% concentration through daily use of cosmetic and household cleaning products. The main route of exposure is expected to be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Irritation
The notified chemical is irritating to skin. The eye irritation potential of the notified chemical is not known. Given the low proposed use concentration (≤ 1%) irritation effects are not expected.

Sensitisation
Based on the results from an LLNA study on an analogue chemical, the notified chemical is considered a weak skin sensitiser (EC3 = 62.5%). Using fine fragrance as an example for products that may contain the notified chemical (at ≤ 1% concentration), as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 37.5 μg/cm^2/day (Cadby *et al.,* 2002). Consideration of available information and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 44.58 μg/cm^2/day. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example of a leave-on cosmetic product) is not considered to be unreasonable. Based on lower expected exposure level from other cosmetic products and household products, by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. However, it is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeated dose toxicity
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products by an individual with total exposure of 0.7204 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 296 mg/kg bw/day derived from a 28 day repeated dose oral toxicity study in rats on an analogue chemical, the margin of exposure (MoE) was estimated to be 411. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Overall, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 1% in fine fragrances, ≤ 0.25% in other cosmetic products, ≤ 1% in fabric care products and ≤ 0.1% in other household products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance formulations for reformulation into finished cosmetic and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. Accident leaks and spills of the product containing the notified chemical are expected to be collected and disposed of to landfill in accordance with local government regulations.

Wastes containing the notified chemical generated from reformulation including equipment wash water, empty import containers and spilt materials (< 1% of the total import volume as indicated by the notifier) are expected to be disposed to on-site waste water treatment or directly to the sewer system. Empty import containers are expected to be recycled or disposed of through licensed waste management services.

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

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated by the notifier that a maximum of 1% of the notified chemical may remain in end-use containers once the consumer products are used up. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate
The notified chemical is readily biodegradable (66% biodegradation in 28 days). For details of the environmental fate study, please refer to Appendix C.

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical will enter into the sewer system before potential release to surface waters nationwide. The notified chemical is expected to partially adsorb to sediment or any suspended particulate matter based on the soil/water adsorption coefficient (log Koc = 2.9 and 3.2) and moderate water solubility. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation and when sewage sludge is used for soil remediation. The notified chemical may also be applied to land when disposed of to landfill as collected spills and empty container residue. The notified chemical in water, landfill, soil and sediment is expected to degrade through biotic and abiotic processes to form water and oxides of carbon. The notified chemical has a low potential to bioaccumulate in aquatic life based on the log Pow of between 3.1 and 3.4.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated assuming that 100% release of the notified chemical into sewer systems nationwide through sewage treatment plants (STPs) and there is no removal of the notified chemical from STPs.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	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 3.74 x 10^{-3} mg/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 1.87 x 10^{-2} mg/kg and 3.74 x 10^{-2} mg/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*
Daphnia Toxicity	48 h EC50 = 6.4 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 10.8 mg/L	Harmful to algae

Based on the above ecotoxicological endpoints, the notified chemical is considered to be toxic to aquatic life. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as “Acute Category 2; Toxic to aquatic life”. Based on the acute toxicity and ready biodegradability of the notified chemical, it is not classified under the Chronic Category.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint (*Daphnia*). An assessment factor of 250 was used given measured acute endpoints from two trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
LC50 (*Daphnia*, 96 h)	6.4 mg/L
Assessment Factor	250
PNEC:	25.6 µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	25.6	**0.022**
Q - Ocean	0.056	25.6	**0.0022**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum use volume and assessed use pattern. The notified chemical is expected to be readily biodegradable and has low potential to bioaccumulate in aquatic life based on the log Pow of 3.1 - 3.4.

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 < -50 °C

Method	OECD TG 102 Melting Point/Melting Range (1995) EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	No freezing of the test substance was observed down to a temperature of -50 °C.
Test Facility	Givaudan (2017a)

Boiling Point 241 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point (1995) EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Siwoloboff capillary tube method.
Test Facility	Givaudan (2017b)

Density 856 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids (2012) EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Oscillating densitometer method.
Test Facility	Givaudan (2017c)

Vapour Pressure 1×10^{-3} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure (2006) EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Gas saturation method.
Test Facility	Givaudan (2017d)

Water Solubility 0.101 g/L at 20 °C

Method	OECD TG 105 Water Solubility (1995) EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	Givaudan (2017e)

Partition Coefficient (n-octanol/water) log Pow = 3.1 and 3.4 at 35 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water) (2004) EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method. Measurement of partition coefficient was conducted at 35 °C due to column temperature. However, the authors of this study state that the obtained values "can be considered to represent values at an unspecified, probably ambient temperature".
Test Facility	Givaudan (2016)

Surface Tension 40.8 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions (1995) EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Concentration: 90.4 mg/L, ~90% saturated solution of the test substance in ultrapure water. Ring method. As the surface tension of the test substance was < 60 mN/m, the test substance was considered surface active.
Test Facility	Givaudan (2017f)

Adsorption/Desorption – screening test log K_{oc} = 2.9 and 3.2 at 35 °C

Method	OECD TG 121 Estimation of the Absorption Coefficient (K_{OC}) on Soil and Sewerage

	Sludge Using High Performance Liquid Chromatography (HPLC) (2001) EC Council Regulation No 440/2008 C.19 Estimation of the Absorption Coefficient (K_{OC}) on Soil and Sewerage Sludge Using High Performance Liquid Chromatography (HPLC)
Remarks	Reverse Phase High Performance Liquid Chromatography method. Measurement of partition coefficient was conducted at 35 °C due to column temperature. However, the authors of this study state that the obtained values "can be considered to represent values at an unspecified, probably ambient temperature".
Test Facility	Givaudan (2017g)

Flash Point 108 °C at 101.3 kPa

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

Flammability Not highly flammable in contact with water

Method	None specified
Remarks	Statement provided by the study authors: from the structural formulae of its constituents GR-50-3010 [the test substance] is not expected to react significantly with water at 20 °C, and will in no way emit flammable gases. This is in line with the fact that during studies such as the determination of the water solubility of GR-50-3010, no reaction of GR-50-3010 with water was reported. Therefore it can be concluded beyond reasonable doubt that the contact of the test substance with water or damp air will not lead to the development of dangerous amounts of gases or gases which may be highly flammable.
Test Facility	Givaudan Int. (2017a)

Autoignition Temperature 250 ± 10 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	None.
Test Facility	Givaudan Int. GSL (2016a)

Explosive Properties No explosive properties

Method	None specified
Remarks	Statement provided by the study authors: from the structural formula of GR-50-3010 [the test substance], it can be concluded that the substance is not explosive. The substance does not have the functional groups associated with explosive properties or chemical instability.
Test Facility	Givaudan Int. (2016a)

Oxidizing Properties No oxidising properties

Method	None specified
Remarks	Statement provided by the study authors: from the structural formula of GR-50-3010 [the test substance], it can be concluded that the substance is not an oxidising substance. The substance does not have the functional groups associated with oxidising properties.
Test Facility	Givaudan Int. (2016b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001) EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method (2008)
Species/Strain	Rat/Wistar (Crl:Han)
Vehicle	None
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	No mortalities occurred during the study. Group 1 animals displayed lethargy, hunched posture, uncoordinated gait, piloerection and salivation for up to 2 hours. Group 2 animals displayed lethargy, hunched and/or flat posture, uncoordinated gait, shallow respiration and ptosis for up to 4 hours.
Effects in Organs	No abnormalities detected at necroscopy.
Remarks - Results	All animals made expected body weight gains during the study.

CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Charles River (2017a)

B.2. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009) EC Council Regulation No 440/2008, B.2 Acute Toxicity (Inhalation)
Species/Strain	Rat/Wistar (Crl:Han)
Vehicle	None
Method of Exposure	Nose-only exposure
Exposure Period	4 hours
Physical Form	Aerosol
Particle Size	MMAD 3.6 µm (both doses)
Remarks - Method	No deviations from the study plan.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5F/5M	2.3	1.2	0/10
2	5F/5M	7.2	5.1	2/10

LC50	> 5.1 mg/L/4 hours
Signs of Toxicity	No mortality or signs of toxicity occurred during treatment at 1.2 mg/L. At 5.1 mg/L, one female was found dead on Day 2 of treatment and one male was sacrificed on Day 3 for ethical reasons.

	All animals treated at 5.1 mg/L displayed lethargy, hunched posture, slow breathing, laboured respiration (9/10 animals) and ptosis. In addition, all males presented with rales, 2/5 females were sneezing and one female had flat posture. All signs of toxicity had regressed by Day 6 of treatment.
Effects in Organs	No abnormalities were noted in animals that survived the treatment period. The male that was sacrificed during treatment presented with yellowish gelatinous contents in the duodenum and gas distension of the jejunum, ileum and caecum. The female that died during treatment displayed early autolysis, dark red pulmonary foci, glandular mucosa and several black-brown foci in the stomach, reddish coloured urinary bladder and reddish foci in the thymus.
Remarks - Results	Body weight loss was noted for all animals on Day 2. This was followed by body weight gains on subsequent days. All females showed expected body weight gains during the study. Males showed reduced body weight gain compared to that expected for rats of this strain and age.
CONCLUSION	The notified chemical is of low acute toxicity via inhalation.
TEST FACILITY	Charles River (2017b)

B.3. Irritation – skin (*in vitro* Reconstructed Human Epidermis Test)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2015) EC Council Regulation No 440/2008 B.46 *In vitro* Skin Irritation: Reconstructed Human Epidermis Model Test (2012)
Vehicle	None
Remarks - Method	No deviations to the study plan were noted. Test system: EPISKIN Small Model. The test substance (25 µL) was applied to the tissues in triplicate. Following an exposure period of 15 minutes at room temperature, the tissues were rinsed and then incubated in fresh medium at 37 °C for 43 hours. The tissues were then treated with MTT and incubated at 37 °C for 3 hours to test for cell viability. Following extraction, the optical densities were determined at 570 nm. The study authors noted that the test substance did not directly interfere with MTT in the preliminary tests. Positive and negative controls were run in parallel with the test substance: - Negative control (NC): PBS - Positive control (PC): Sodium dodecyl sulphate (5%)

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.919	100	1.1
Test substance	0.042	4.5	0.78
Positive control	0.099	11	2.5

OD = optical density; SD = standard deviation

Remarks - Results	The positive and negative controls performed as expected, confirming the validity of the test system.
CONCLUSION	The viability of the notified chemical was ≤ 50%, indicating the notified chemical was irritating to the skin under the conditions of the test.
TEST FACILITY	Charles River (2016a)

B.4. Corrosion – skin (*in vitro* Reconstructed Human Epidermis Test)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 *In vitro* Skin Corrosion: Reconstructed Human *Epidermis* Test Method (2016) EC Council Regulaion No 440/2008 B.40 *In vitro* Skin Corrosion: Human Skin Model Test (2008)
Vehicle	None
Remarks - Method	No deviations to the study plan were noted. Test system: EpiDerm Skin Model. The test substance (50 µL) was applied to the tissues in duplicate. Following exposure periods of 3 minutes (room temperature; test 1) and 1 hour (37 °C; test 2), the tissues were rinsed, treated with MTT and incubated (37 °C, 3 hours) to test cell viability. After extraction, optical densities were determined at 570 nm. The study authors noted that preliminary tests had been conducted, which indicated that the test substance does not directly interfere with MTT. Positive and negative controls were run in parallel with the test substance: - Negative control (NC): Milli-Q water - Positive control (PC): Potassium hydroxide (8M)

RESULTS

Test material	*Test 1 (3 minute exposure period)*		*Test 2 (1 hour exposure period)*	
	Mean OD_{570} of duplicate tissues	*Relative mean viability (%)*	*Mean OD_{570} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.524	100	1.543	100
Test substance	2.052	135	1.966	127
Positive control	0.182	12	0.133	9

OD = optical density

Remarks - Results	The positive and negative controls performed as expected and variation between tissue replicates was within acceptable range, confirming the validity of the test system.
CONCLUSION	The viability of the notified chemical was ≥ 50% after 3 minutes exposure and ≥ 15% after 1 hour exposure, indicating that the notified chemical is non-corrosive to the skin under the conditions of the test.
TEST FACILITY	Charles River (2017c)

B.5. Irritation – eye (*in vitro* Bovine Corneal Opacity and Permeability Test)

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

(2013)

Vehicle: None

Remarks - Method: No significant protocol deviations. Corneas were exposed to the test substance for 10 minutes at 32 °C. Physiological saline was used as a negative control and ethanol (> 99%) was used as a positive control.

RESULTS

Test material	*Mean opacities of triplicate tissues*	*Mean permeabilities of triplicate tissues*	*IVIS*
Negative control	1.1	0.004	1.2
*Test substance**	8.2	0.213	11.4
*Positive control**	19.9	1.690	45.3

IVIS = *in vitro* irritancy score
*Corrected for background values

Remarks - Results: Corneas treated with the test substance appeared slightly translucent and contained small spots after treatment.

The test substance resulted in an IVIS of 11.4. Under the study guidelines, no prediction can be made for IVIS > 3 and ≤ 55.

CONCLUSION: No prediction could be made for the test substance under test conditions.

TEST FACILITY: Charles River (2017d)

B.6. *In Chemico* Skin Sensitisation (DPRA Test)

TEST SUBSTANCE: Notified chemical

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

Vehicle: Acetonitrile

Remarks - Method: No significant deviations from the study method.

The test substance was prepared in acetonitrile (100 mM solution). Cinnamic aldehyde (100 mM in acetonitrile) was used as a positive control. Solvent reference controls were setup and run in parallel to the test substance. 0.5 mM solutions of cysteine and lysine peptides were prepared in phosphate (pH 7.4) and ammonium acetate (pH 10.5) buffers respectively. The test substance was incubated with the peptide solutions for 24 hours at 30 °C. The ratios of test substance: peptides were 1:10 and 1:50 for cysteine and lysine peptides respectively. Peptide depletion was then monitored by HPLC coupled with UV detection at 220 nm.

In a preliminary study, it was determined that the vehicle had minimal effect on peptide stability.

RESULTS

Sample	*Cysteine Peptide Depletion (% ± SD)*	*Lysine Peptide Depletion (% ± SD)*
Vehicle	0.0*	0.0*
Test Substance	0.8 ± 1.4	0.3 ± 0.4
Positive Control	65.9 ± 0.7	50.7 ± 2.8

* – normalised to 100%; SD = Standard Deviation

Remarks - Results: The reactivity of the test substance, measured as % peptide depletion, was less than the cut-off value for minimal reactivity i.e. < 6.38%.

The positive controls and references performed as expected, confirming the validity of the test.

CONCLUSION	The notified chemical was considered to have no or minimal reactivity under the conditions of the test for peptide depletion, the first key event in the adverse outcome pathway (AOP) for skin sensitisation.
TEST FACILITY	Givaudan Schweiz (2017a)

B.7. *In Vitro* Skin Sensitisation (ARE-Nrf2 Luciferase Test)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 442d *In Vitro* Skin Sensitisation: ARE-Nrf2 Luciferase Test Method (2015)
Vehicle	DMSO (1%)
Remarks - Method	No significant deviations from the study plan were noted. A 200mM stock solution of test substance was prepared in DMSO. A set of twelve solutions were prepared in DMSO from the stock solution (conc. range 0.98 – 2000 µM). The KeratinoSens cell line was treated with the test substance for 48 hours. DMSO and cinnamic aldehyde were used in parallel with the test substance as negative and positive controls respectively. Three independent experiments were conducted with samples tested in triplicate in each experiment. Cell viability was determined for each replicate using the MTT assay. Skin sensitisation was measured as luciferase induction, calculated from three independent experiments.

RESULTS

Sample	*Cell viability – IC50 (µM) (mean* ± SD)*	*Luciferase I_{MAX} (maximum average fold induction of luciferase activity) (mean* ± SD)*
Test substance	190.11 ± 3.9	1.21 ± 0.07

*from three independent experiments conducted in triplicate
IC50 = Concentration for 50% reduction in cell viability
I_{MAX} = Maximal fold-gene induction of the reporter gene up to 1000 µM concentration

Remarks - Results	The authors of this study considered the test substance to be moderately cytotoxic under the conditions of the test. The test substance did not induce an I_{MAX} greater than 1.5 fold threshold and so was rated negative. The positive control and vehicle performed as expected, confirming the validity of the test.
CONCLUSION	The notified chemical was negative under the conditions of the test for the second key event in the AOP for skin sensitisation.
TEST FACILITY	Givaudan Schweiz (2017b)

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

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/J
Vehicle	Acetone/olive oil (4:1)
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method	No significant protocol deviations

RESULTS

Test substance concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
0 (vehicle control)	5F	423 (± 46)	-
25%	5F	922 (± 147)	2.2
50%	5F	1129 (± 156)	2.7
100%	5F	1647 (± 313)	3.9

EC3 62.5%

Remarks - Results In the preliminary study, no signs of systemic toxicity or irritation (the latter indicated by < 25% increase in mean ear thickness) were noted.

In the main study, there were no mortalities or signs of systemic toxicity observed in the test or control animals. Slight irritation was noted on the ears of animals treated with the test substance at 100% concentration on Days 2-4.

The auricular lymph nodes of the animals in control, 25% and 50% concentration groups were considered of normal size while nodes of the animals in 100% concentration group were considered enlarged. No macroscopic abnormalities of the surrounding area were seen for any animals.

The test substance elicited a stimulation index ≥ 3 and is therefore considered a skin sensitiser.

All treated animals showed comparable body weight changes to those of the vehicle control group.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance under the conditions of the test.

TEST FACILITY WIL (2015a)

B.9. Repeat dose toxicity

TEST SUBSTANCE Analogue chemical: Cyclopropanemethanol, 2-(1,4-dimethyl-3-penten-1-yl)-1-methyl- (CAS No: 1655500-83-6)

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain Rat/Crl:WI (Han)

Route of Administration Oral – diet

Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 14 days

Vehicle None

Remarks - Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose ppm (mg/kg bw/day)*	*Mortality*
control	5 per sex	0	0/10
control recovery	5 per sex	0	0/10
low dose	5 per sex	1,000 (98 for males and females)	0/10
mid dose	5 per sex	3,000 (296 for males and 300 for females)	0/10
high dose	5 per sex	10,000 (1,011 for males and 944 for females)	0/10
high dose recovery	5 per sex	10,000 (1,011 for males and 944 for females)	0/10

Mortality and Time to Death
No unscheduled deaths occurred.

Clinical Observations
No clinical signs or toxicologically significant changes were noted in clinical appearance and functional observations.

Both sexes treated with 10,000 ppm showed slightly lower body weight, consistent with slightly lower food consumption in Week 1. At the end of recovery period, the male animals showed higher body weight accompanied with slightly higher food consumption. Male animals treated with 3,000 ppm showed incidentally slightly higher body weight. These findings were not considered by the study authors to be toxicologically relevant as these changes were slight and/or reversible.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Male and female animals treated with 10,000 ppm showed a lower red blood cell count, lower haemoglobin and haematocrit levels, lower total protein and albumin levels, a lower total bilirubin level (also for animals treated with 3,000 ppm), lower glucose and bile acid levels and a higher cholesterol level. Red blood cell metabolism showed recovery at the end of the recovery period as a higher red cell distribution width and a mean corpuscular volume were noted. These changes in haematological and clinical biochemical parameters were not considered by the study authors to be adverse given they were slight and/or reversible and not supported by any related morphological changes.

Effects in Organs
Tubular degeneration, papillary cysts, tubular dilation and hyperplasia of the pelvic urothelium in the kidneys of male animals treated with 10,000 ppm were considered by the study authors to be adverse given the changes were indicators of toxicity and there were no signs of recovery at the end of the recovery period.

Hepatocellular hypertrophy combined with a slight increase in the relative liver weight in both sexes treated with 10,000 ppm was not considered by the study authors to be adverse due to the absence of any other indicators of hepatocellular toxicity and the complete recovery at the end of the recovery period.

Increased incidence and/or severity of follicular cell hypertrophy noted in the thyroid gland of both sexes treated with 10,000 ppm were considered by the study authors to be adaptive changes and non-adverse.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 3,000 ppm (equivalent to 296 mg/kg bw/day for males and 300 mg/kg bw/day for females) in this study, based on the morphological changes in the kidney of male animals at the higher dose

TEST FACILITY	WIL (2015b)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical	
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria (2008) Plate incorporation procedure	
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA	
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver.	
Concentration Range in Main Test	<u>Test 1</u> a) With metabolic activation:	5.4 - 5000 µg/plate
	b) Without metabolic activation:	5.4 - 5000 µg/plate
	<u>Test 2</u> a) With metabolic activation:	1.7 - 1600 µg/plate (*S. typhimurium* strains)

52 – 5000 µg/plate (*E. coli* strains)

b) Without metabolic activation: 1.7 - 512 µg/plate (*S.typhimurium* strains)
52 – 5000 µg/plate (*E. coli* strains)

Vehicle: DMSO

Remarks - Method: No significant deviations from the study plan. A preliminary experiment was conducted to determine the dose range for the main test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 164	-	≥ 512	Negative
Test 2	-	≥ 512	≥ 512	Negative
Present				
Test 1	≥ 512	-	≥ 512	Negative
Test 2	-	≥ 164	≥ 512	Negative

Remarks - Results: No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with the test substance at any dose level, in the presence or absence of metabolic activation. Vehicle and positive controls performed as expected, confirming the validity of the test system.

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

TEST FACILITY: Charles River (2017e)

B.11. Genotoxicity – *in vitro* mammalian cell gene mutation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 487 *In vitro* Mammalian Cell Micronucleus Test (2016)

Species/Strain: Human

Cell Type/Cell Line: Peripheral lymphocyte

Metabolic Activation System: S9 fraction from phenobarbital/β-napthoflavone induced rat liver

Vehicle: DMSO

Remarks - Method: Preliminary experiments were conducted to determine the dose range for the main study.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1 (preliminary)	31, 63, 125, 250, 500, 1000	3 h	27 h
Test 2 (preliminary)	31, 63, 125, 250, 500, 1000	24 h	24 h
Test 3	100, 125, 150, 175, 200, 225	3 h	27 h
Test 4	25*, 100, 110*, 120, 130, 140*, 150	3 h	27 h
Test 5	10,* 20, 30*, 40*, 50, 60, 70	24 h	24 h
Present			
Test 1 (preliminary)	31, 63, 125, 250, 500, 1000	3 h	27 h
Test 2	-	-	-
Test 3	100, 125, 150, 175, 200, 225	3 h	27 h
Test 4	25*, 100, 120, 130, 140*, 150*, 160, 170	3 h	27 h
Test 5	-	-	-

*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	≥ 250	-	≥ 500	ND
Test 2	≥ 31	-	≥ 500	ND
Test 3	-	≥ 125	> 225	ND
Test 4	-	≥ 140	> 150	Negative
Test 5	-	≥ 30	> 70	Negative
Present				
Test 1	≥ 250	-	≥ 500	ND
Test 2	-	-	-	-
Test 3	-	≥ 150	> 225	ND
Test 4	-	≥ 120	> 170	Negative
Test 5	-	-	-	-

ND: Not determined

Remarks - Results

The dose ranges for Test 3 in the absence or presence of metabolic activation were based on the results of the preliminary tests. Test 3 cultures displayed cytotoxicity at the second lowest test substance dose in the presence or absence of metabolic activation. Hence, no appropriate dose levels could be selected for scoring of micronuclei.

The experiment was repeated using a narrower range of doses (Test 4). In the absence and presence of metabolic activation, the test substance did not induce a biologically relevant increase in the number of mono- and binucleated cells containing micronuclei.

Test 5 was conducted to obtain more information about the potential genotoxicity of the test substance by exposing cells to the test substance for 24 hours in the absence of metabolic activation. The test substance did not induce a biologically relevant increase in the number of mono- and binucleated cells containing micronuclei.

Vehicle and positive controls performed as expected, confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Charles River (2017f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test (1992) EC Directive 2008/440/EC C.4 Determination of "Ready" Biodegradability, Part V., Manometric Respirometry Test (Method C.4-D)
Inoculum	Activated sludge
Exposure Period	61 days
Auxiliary Solvent	No
Analytical Monitoring	Oxygen consumption
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Toxicity control was not conducted in parallel. However, this is not considered to affect the validity of the study.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	4	5	62
7	10	7	72
17	58	14	77
21	62	21	80
28	66	28	79
42	72	61	75
61	75		

Remarks - Results	The test substance undergoes 66% biodegradation after 28 days. However, the 10 window criterion was not met. The OECD 301 guidelines related to biodegradation indicates that mixtures and isomers in their most purified forms expect a sequential biodegradation and hence for such mixtures the 10 day does not apply. Therefore, the notified chemical is considered to be readily biodegradable. All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 72% by 7 days and reached 79% degradation by 28 days. Therefore, the test indicates the suitability of the inoculums.
CONCLUSION	The notified chemical is readily biodegradable
TEST FACILITY	Givaudan (2017i)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static (2004) EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia -

	Semi-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 study was conducted according to the above guidelines without deviation from the protocol. The test media were renewed every 24 hours.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	-	20	0	0
1.0	0.84	20	0	0
2.2	1.9	20	0	0
5.0	4.1	20	0	2
11	7.5	20	1	3
25	17	20	8	20

EC50	3.4 mg/L at 48 hours (95% confidence limits, 3.0 – 3.7 mg/L). Statistical analysis was performed using ToxRat Professional®.
Remarks - Results	In the control, no daphnids showed immobilization or other signs of disease or stress (e.g., discolouration or unusual behaviour such as trapping at the surface of water). As such, the test is considered to be valid. Furthermore, the dissolved oxygen concentration at the end of the test was ≥ 3 mg/L in all test vessels. The measured concentrations of the test substances were less than 80% of the nominal concentrations. Therefore, results are based on mean measured concentrations.

CONCLUSION The notified chemical is toxic to aquatic invertebrates

TEST FACILITY IES (2017a)

C.2.2. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test (2006)
EC Council Regulation No 440/2008 C.3 Algal Inhibition Test (2016)

Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: Control, 0.50, 1.6, 5.0, 16 and 50 mg/L Actual: 0.21, 0.91, 3.0, 11 and 36 mg/L
Auxiliary Solvent	None
Water Hardness	15 mg/L $CaCO_3$
Analytical Monitoring	Gas chromatography
Remarks - Method	The study was conducted according to the above guidelines without deviation from the protocol.

RESULTS

Biomass		*Growth*	
EC50 *mg/L at 72 h*	*NOEC* *72 mg/L*	*EC50* *mg/L at 72 h*	*NOEC* *72 mg/L*
6.1	1.02	10.8	1.02

Remarks - Results	The validity criteria for increase of biomass, mean coefficient of variation of the daily growth rates and coefficient of variation of the average

	specific growth rates were fulfilled. The measured concentrations of the test substances were less than 80% of the nominal concentrations. Therefore, results are based on mean measured concentrations.
CONCLUSION	The notified chemical is harmful to algae
TEST FACILITY	IES (2017b)

BIBLIOGRAPHY

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

Cadby, P.A., Troy, W.R., Vey, M.G.; Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation, Regulatory Toxicology and Pharmacology 36 (2002) 246-252.

Charles River (2016a) *In vitro* Skin Irritation Test with GR-50-3010 using a Human Skin Model (Study No. 515951, December, 2016). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017a) Assessment of Acute Oral Toxicity with GR-50-3010 in the Rat (Acute Toxic Class Method) (Study No. 515949, January, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017b) Assessment of Acute Inhalation Toxicity with GR-50-3010 in the Rat (nose-only) (Study No. 515950, March, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017c) *In vitro* Skin Corrosion Test with GR-50-3010 using a Human Skin Model (Study No. 517145, March, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017d) Evaluation of the Eye Hazard Potential of GR-50-3010 using the Bovine Corneal Opacity and Permeability Test (BCOP Test) (Study No. 515952, January, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017e) Evaluation of the Mutagenic Activity of GR-50-3010 in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (Study No. 515953, March, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (Unpublished report submitted by the notifier).

Charles River (2017f) An i*n vitro* Micronucleus Assay with GR-50-3010 in Cultured Peripheral Human Lymphocytes (Study No. 515954, April, 2017). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch B.V. (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.

Givaudan (2016) Partition Coefficient n-Octanol/Water of GR-50-3010 (Study No. 16-E257, December, 2016). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017a) Freezing Point of GR-50-3010 (Study No. 16-E260, March, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017b) Boiling Point of GR-50-3010 (Study No. 16-E261, April, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017c) Density of GR-50-3010 (Study No. 16-E265, May, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017d) Vapour Pressure of GR-50-3010 (Study No. 16-E268, March, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017e) Water Solubility of GR-50-3010 (Study No. 16-E262, March, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017f) Surface Tension of an Aqueous Solution of GR-50-3010 (Study No. 16-E263, March, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017g) Adsorption Coefficient of GR-50-3010 (Study No. 16-E264, June, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017h) Flash Point of GR-50-3010 (Study No. 16-E259, March, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan (2017i) Ready Biodegradability of GR-50-3010 (Study No. 16-E256, May, 2017). Geneva, Switzerland, Givaudan Suisse SA Ecotoxicological Laboratory (Unpublished report submitted by the notifier).

Givaudan Int. (2016a) Expert Statement on the explosive properties of GR-50-3010 (Study No. 16-E269/S, November, 2016). Geneva, Switzerland, Givaudan International SA Regulatory Affairs and Product Safety (Unpublished report submitted by the notifier).

Givaudan Int. (2016b) Expert Statement on the oxidising properties of GR-50-3010 (Study No. 16-E268/S, November, 2016). Geneva, Switzerland, Givaudan International SA Regulatory Affairs and Product Safety (Unpublished report submitted by the notifier).

Givaudan Int. (2017a) Expert Statement on the flammability (contact with water) of GR-50-3010 (Study No. 16-E267/S, May, 2017). Geneva, Switzerland, Givaudan International SA Regulatory Affairs and Product Safety (Unpublished report submitted by the notifier).

Givaudan Int. GSL (2016a) Auto-ignition temperature of GR-50-3010 (Study No. 2016-570, December, 2016). Geneva, Switzerland, Givaudan International Global Safety Laboratory (Unpublished report submitted by the notifier).

Givaudan Schweiz (2017a) Direct Peptide Reactivity Assay (DPRA): Test Report on GR-50-3010-30 (Study No. RCR 153'667, March, 2017). Dübendorf, Switzerland, *In Vitro* Toxicology Laboratory Givaudan Schweiz AG (Unpublished report submitted by the notifier).

Givaudan Schweiz (2017b) KeratinoSens Assay (DPRA): Test Report on GR-50-3010-30 (VE00466805) (Study No. RCR 153'666, March, 2017). Dübendorf, Switzerland, *In Vitro* Toxicology Laboratory Givaudan Schweiz AG (Unpublished report submitted by the notifier).

IES (2017a) GR-50-3010 - Acute Toxicity to *Daphnia magna* in a 48-Hour Immobilization Test (Study No. 20160320, April, 2017). Witterswil, Switzerland, Innovative Environmental Services (IES) Ltd (Unpublished report submitted by the notifier).

IES (2017b) GR-50-3010 – Effect of *Pseudokirchneriella subcapitata* in a 72-Hour Algal Growth Inhibition Test (Study No. 20160319, April, 2017). Witterswil, Switzerland, Innovative Environmental Services (IES) Ltd (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.

OECD (2016) Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, Series on Testing and Assessment No. 256, Organisation for Economic Co-Operation and Development (OECD).

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) Notes of Guidance for testing of Cosmetic Ingredients 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.

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

WIL (2015a) Assessment of Contact Hypersensitivity to GR-50-1408 in the Mouse (Local Lymph Node Assay) (Study No. 507509, March, 2015). DD 's-Hertogenbosch, The Netherlands, WIL Research Europe B.V. (Unpublished report submitted by the notifier).

WIL (2015b) 28-Day Oral Toxicity Study with GR-50-1408 by Dietary Administration in the Rat Followed by a 14-Day Recovery Period (Study No. 507512, August, 2015). DD 's-Hertogenbosch, The Netherlands, WIL Research Europe 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 >