File No: LTD/1926

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclopropanemethanol, 2-(1,4-dimethyl-3-penten-1-yl)-1-methyl-

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:

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1926	Givaudan Australia Pty Ltd	Cyclopropanemethanol, 2-(1,4-dimethyl-3-penten-1-yl)-1-methyl-	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*
Acute toxicity, dermal (Category 4)	H312 – Harmful in contact with skin
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage/eye irritation (Category 2A)	H319 – Causes serious eye irritation
Skin sensitisation (Category 1)	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
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

Based on the available information, when used at ≤ 0.3% concentration in fine fragrances, at ≤ 0.12% concentration in other cosmetics or at ≤ 0.02% concentration in household products, 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 assessed 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:
  - Acute toxicity, dermal (Category 4): H312 – Harmful in contact with skin
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Serious eye damage/eye irritation (Category 2A): H319 - Causes serious eye irritation

- Skin sensitisation (Category 1): 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 and the intended use/exposure scenario.

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 isolation and 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 and eyes
  - Avoid inhalation

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Coveralls
  - Impervious gloves
  - Eye protection
  - Respiratory protection, if inhalation exposure may occur

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

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.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by 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 0.3% in fine fragrances, 0.12% in other cosmetics or 0.02% in household products;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
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 (2015), EU (2015), Switzerland (2015), USA (2015)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Rosyfolia

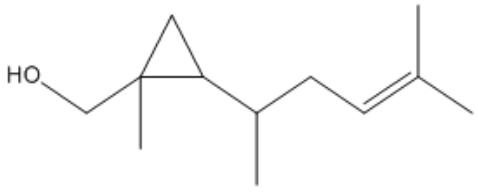
CAS NUMBER
1655500-83-6

CHEMICAL NAME
Cyclopropanemethanol, 2-(1,4-dimethyl-3-penten-1-yl)-1-methyl-

OTHER NAME(S)
GR-50-1408

MOLECULAR FORMULA
$C_{12}H_{22}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
182.3 Da

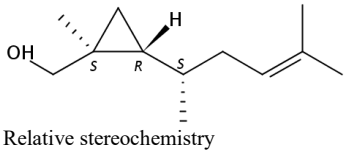
ANALYTICAL DATA
Reference NMR, IR, GC-MS and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 80%

^{1}H NMR and GC-MS indicate that the notified chemical is mainly composed of two diastereoisomers (A and B) in an approximate molar ratio of 3:2, respectively.

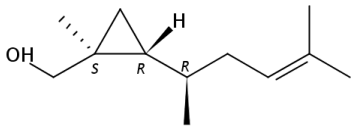
Diastereoisomer A



Relative stereochemistry

Cyclopropanemethanol, 2-[(1R)-1,4-dimethyl-3-penten-1-yl]-1-methyl-, (1R,2S)-rel-
CAS No. 1414398-09-6

Diastereoisomer B



Relative stereochemistry

Cyclopropanemethanol, 2-[(1R)-1,4-dimethyl-3-penten-1-yl]-1-methyl-, (1S,2R)-rel-
CAS No. 1414398-10-9

IDENTIFIED IMPURITIES

Chemical Name	2,6-Octadien-1-ol, 2,4,7-trimethyl-, (2*E*)-		
CAS No.	1414398-07-4	*Weight %*	1.59
Chemical Name	Oct-6-en-1-ol, 2,4,7-trimethyl-		
CAS No.	Unassigned	*Weight %*	1.57
Chemical Name	Diastereomer of 2-((1*S*,2*S*)-2-methyl-2-(3-methylbut-2-en-1-yl)cyclopropyl)propan-1-ol, *rel*-		
CAS No.	Unassigned	*Weight %*	1.14
Chemical Name	Diastereomeric pair of ((1*S*,2*R*)-2-((2*S*)-1-(2,2-dimethylcyclopropyl)propan-2-yl)-1-methylcyclopropyl)methanol, *re*l-		
CAS No.	Unassigned	*Weight %*	4.14
Chemical Name	Diastereomeric pair of ((1*S*,2*R*)-2-((2*R*)-1-(2,2-dimethylcyclopropyl)propan-2-yl)-1-methylcyclopropyl)methanol, *re*l-		
CAS No.	Unassigned	*Weight %*	1.11

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: liquid

Property	Value	Data Source/Justification
Freezing Point	< -50 °C	Measured
Boiling Point	257 °C at 101.3 kPa	Measured
Density	880 kg/m^3 at 20 °C	Measured
Vapour Pressure	5×10^{-4} kPa at 20 °C	Measured
Water Solubility	7×10^{-2} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ > 365 day at pH 4, 7 and 9	Measured

Property	Value	Data Source/Justification
Partition Coefficient (n-octanol/water)	log Pow = 3.5 at 35 °C	Measured
Surface Tension	38.6 mN/m at 20 °C	Measured
Adsorption/Desorption	log Koc = 3.14 at 35 °C	Measured
Dissociation Constant	Not determined	Not expected as the chemical does not contain dissociable functionalities
Flash Point	105.5 °C at 101.3 kPa	Measured
Flammability	Not expected to be highly flammable	Estimated based on chemical structure
Autoignition Temperature	250 °C	Measured
Explosive Properties	Predicted negative	Estimated based on chemical structure
Oxidising Properties	Predicted negative	Estimated based on chemical 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 not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured within Australia. The notified chemical will be imported into Australia as a component of fragrance formulations at ≤ 2.4% concentration.

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

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

PORT OF ENTRY
Sydney (via sea or air) and Perth (via air)

IDENTITY OF MANUFACTURER/RECIPIENTS
Givaudan Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of fragrance formulations at ≤ 2.4% concentration in glass, lacquer-lined containers of sizes ranging 1-190 kg. Finished consumer products containing ≤ 0.3% notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a component of fragrance ingredient in cosmetic and household products (at ≤ 0.3% concentration in fine fragrances, at ≤ 0.12% concentration in other cosmetics and at ≤ 0.02% concentration in household products).

OPERATION DESCRIPTION
The notified chemical will be imported as a component of fragrance formulations at ≤ 2.4% concentration for reformulation into cosmetic and household products.

Reformulation
The procedures for reformulating the fragrance formulations containing the notified chemical will likely vary depending on the nature of the cosmetic/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
The finished products containing the notified (at ≤ 0.3% concentration in fine fragrances, at ≤ 0.12% concentration in other cosmetics and at ≤ 0.02% concentration in household products) may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the products, these could be applied in a number of ways, such as by hand, using an applicator or by spray.

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	unknown
Mixing	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	4	2
Packaging	4	2
Professional end users	not specified	not specified

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may come in contact with the notified chemical either at ≤ 2.4% concentration in fragrance formulations or at ≤ 0.3% concentration in consumer products only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into consumer products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 2.4% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End-use
Exposure to the notified chemical in end-use products at ≤ 0.3% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons), or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such workers 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 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 ≤ 0.3% concentration through the use of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of the exposure assessment, 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	0.12	1	0.1466
Face cream	1540	0.12	1	0.0289
Hand cream	2160	0.12	1	0.0405
Fine fragrances	750	0.3	1	0.0352
Deodorant spray	1430	0.12	1	0.0281
Shampoo	10460	0.12	0.01	0.0020
Conditioner	3920	0.12	0.01	0.0007
Shower gel	18670	0.12	0.01	0.0035
Hand soap	20000	0.12	0.01	0.0038
Hair styling products	4000	0.12	0.1	0.0075
Total				0.2967

C = concentration of the 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	0.02	0.95	10	0.0007
Fabric softener	90	0.02	0.95	10	0.0003
Total					0.0010

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	0.02	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.02	1980	0.0093	0.01	0.03	0.0001
All-purpose cleaner	1	0.02	1980	1	0.01	0.007	0.0004
Total							0.0005

Daily systemic exposure = (Frequency × C × Contact Area × Product Usage × Film Thickness on skin × Time Scale Factor × DA)/BW

Aerosol products (Inhalation exposure)

Product type	Amount	C	Inhalation Rate	Exposure Duration (Zone 1)	Exposure Duration (Zone2)	Fraction Inhaled	Volume (Zone 1)	Volume (Zone 2)	Daily systemic exposure
	(g/day)	(%)	(m^3/day)	(min)	(min)	(%)	(m^3)	(m^3)	(mg/kg bw/day)
Hairspray	9.89	0.12	20	1	20	50	1	10	0.0039

Daily systemic exposure = [(Amount × C × Inhalation Rate × Fraction Inhaled × 0.1) / BW × 1440)] × [Exposure Duration (Zone 1)/Volume (Zone 1) + Exposure Duration (Zone 2)/Volume (Zone 2)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 0.3021 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of 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).

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 dermal toxicity	LD50 = 1000 - 2000 mg/kg bw; harmful
Skin irritation (in vitro)	irritating
Eye irritation (in vitro)	irritating
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation (EC3 = 62.5%)
Rat, repeat dose oral toxicity – 28 days	NOAEL = 3000 ppm
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic

Toxicokinetics

Based on the low molecular weight (< 500 Da), water solubility (7×10^{-2} mg/L at 20 ºC) and partition coefficient (log Pow = 3.5 at 35 °C) of the notified chemical, there is potential for the chemical to cross biological membranes.

Acute toxicity

The notified chemical was found to be of low toxicity via the oral route in a study conducted in rats.

The notified chemical was found to be harmful via the dermal route in a study conducted in rats. Three of five female animals and one of five male animals treated with 2,000 mg/kg bw died. There were no mortalities for animals treated with 1,000 mg/kg bw. As female is generally the appropriate sex of test animals for the OECD test, the LD50 is therefore considered to be 1,000 – 2,000 mg/kg bw.

Irritation

In an *in vitro* skin irritation study conducted using the reconstructed human epidermis model (EpiSkin™), the notified chemical was determined to be irritating to the skin. In an *in vitro* bovine corneal opacity and permeability (BCOP) test the notified chemical was determined to be irritating to eyes. Although no prediction on the classification was made in the eye irritation study, the notified chemical is classified as H319 - Causes serious eye irritation by the notifier.

Sensitisation

The notified chemical was a skin sensitiser in mice (local lymph node assay: stimulation indices of 2.2, 2.7 and 3.9 at 25%, 50% and 100%, respectively). The EC3 value was calculated to be 62.5%.

Repeated dose toxicity

A repeated dose oral (diet) toxicity study on 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.

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 morphological changes in the kidney of males (tubular degeneration, papillary cysts, tubular dilation and hyperplasia of the pelvic urothelium) in the high dose group.

Mutagenicity/Genotoxicity

The notified chemical was negative in a bacterial reverse mutation assay and in an *in vitro* mammalian chromosome aberration 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*
Acute toxicity, dermal (Category 4)	H312 – Harmful in contact with skin
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage/eye irritation (Category 2A)	H319 – Causes serious eye irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available toxicological information and use pattern, the critical health effects of the notified chemical are harmful in contact with skin and as a skin and eye irritant and a skin sensitiser. Adverse effects could also occur after repeated exposure.

Reformulation
During reformulation, workers may be at risk of acute dermal toxicity and skin sensitisation effects when handling the notified chemical at ≤ 2.4% concentration. It is anticipated by the notifier 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 and household products containing the notified chemical to clients (*e.g.*, hairdressers, beauty salon workers and cleaners) may be exposed to the notified chemical at concentrations up to 0.3%. 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 at ≤ 0.3% concentration will be available to the public. The main route of exposure is expected to be dermal and inhalation, with some potential for accidental ocular or oral exposure.

Acute toxicity
The notified chemical is harmful in contact with skin and a skin and eye irritant. However, these effects are not expected from use of the notified chemical at the proposed low concentrations in cosmetic and household products.

Sensitisation
When tested in an LLNA study, the notified chemical was considered as 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). Using fine fragrance as an example for products that may contain the notified chemical (at ≤ 0.3% concentration), as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 11.25 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 47.86 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 repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.3021 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 on the notified chemical, the margin of exposure (MoE) was estimated to be 979. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. Therefore, the MoE is considered to be acceptable.

Therefore, the risk to the public from use of the notified chemical at ≤ 0.3% concentration in fine fragrances, at ≤ 0.12% concentration in other cosmetics and at ≤ 0.02% concentration in household products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified 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 is expected to be collected and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will occur within a fully enclosed system. Therefore, significant release of the notified chemical from this process to the environment is not expected. 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 of to on-site waste water treatment or directly to 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 import volume 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 not readily biodegradable (22% biodegradation in 28 days) or inherently biodegradable (33% biodegradation in 60 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 = 3.14) and low water solubility. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation, when sewage sludge is used for soil remediation. The notified chemical may also be applied to land when disposed of to landfill as collected spills and empty container

residue. The notified chemical in water, landfill, soil and sediment is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical has a potential to bioaccumulate in aquatic life based on the relatively high log Pow = 3.5. However, the notified chemical does not meet the bioaccumulative criterion of a PBT chemical.

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)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	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 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.39 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 3.2 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 = 3.4 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 E_rC50 = 8.6 mg/L	Toxic to algae
Inhibition of Bacterial Respiration	3 h EC50 > 100 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints for the notified chemical, it 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 not ready biodegradability of the notified chemical, it is formally classified as "Chronic Category 2; Toxic to aquatic life" under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint of LC50 = 3.2 mg/L for fish. An assessment factor of 100 was used given measured acute endpoints from three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
LC50 (fish, 96 h)	3.2 mg/L
Assessment Factor	100
PNEC:	32 µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	32	**0.019**
Q - Ocean	0.061	32	**0.0019**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum use volume and assessed use pattern. The notified chemical is not expected to be readily biodegradable or significantly bioaccumulate in the environment.

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.
Remarks Determined using a crystallising apparatus.
Test Facility Givaudan (2014a)

Boiling Point 257 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Remarks Siwoloboff Method
Test Facility Givaudan (2013a)

Density 880 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Oscillating densitimeter method
Test Facility Givaudan (2013b)

Vapour Pressure 5×10^{-4} kPa at 20 °C

Method OECD TG 104 Vapour Pressure.
Remarks Gas saturation method
Test Facility Givaudan (2013c)

Water Solubility 7×10^{-2} g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method
Test Facility Givaudan (2014b)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ days*
4	25	> 365
7	25	> 365
9	25	> 365

Remarks In the preliminary tests, less than 10% hydrolysis was determined for the test substance at 50 °C at pH values of 4, 7 and 9, corresponding to a half-life time of more than 1 year according to the test guideline. Therefore, only preliminary tests were conducted in this study. The notified chemical is expected to be hydrolytically stable.
Test Facility Givaudan (2014c)

Partition Coefficient (n-octanol/water) log Pow = 3.5 at 35 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method
Test Facility Givaudan (2013d)

Surface Tension 38.6 mN/m at 20 °C

Method OECD TG 115 Surface Tension of Aqueous Solutions.
Remarks Concentration: ~81% of the saturation concentration.
Test Facility Givaudan (2014d)

Adsorption/Desorption – screening test

log K_{oc} = 3.14 at 35 °C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks	Reverse High Performance Liquid Chromatography method
Test Facility	Givaudan (2013e)

Flash Point

105.5 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method
Test Facility	Givaudan (2013f)

Autoignition Temperature

250 ± 10 °C

Method	DIN 51794
Remarks	Determined in a SUR BERLIN oven
Test Facility	Givaudan (2013g)

Appendix B: Toxicological Investigations

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.
- Species/Strain: Rat/Wistar
- Vehicle: None
- Remarks - Method: No significant protocol deviations. A pilot study was conducted in a female animal at a dose of 2000 mg/kg bw. The dose was selected for the main study based on the results of the pilot study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1F	2000	0/1
2	4F	2000	0/4

- LD50: > 2000 mg/kg bw
- Signs of Toxicity: Signs of systemic toxicity including hunched posture and/or piloerection were noted in all animals between Days 1 and 7. One animal also showed flat posture, laboured respiration, lean appearance and ptosis on Day 1and/or 2.
- Effects in Organs: No abnormalities were noted at macroscopic examination.
- Remarks - Results: The animals showed expected body weight gain over the observation period.

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

TEST FACILITY: WIL (2015a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 402 Acute Dermal Toxicity.
- Species/Strain: Rat/Wistar Crl:WI (Han)
- Vehicle: None
- Type of dressing: Semi-occlusive
- Remarks - Method: No significant protocol deviations. The study was initially conducted in 10 animals at a dose of 2000 mg/kg bw. Due to the number of deaths (4/10) at the 2000 mg/kg bw dose level, an additional group of 5 female animals was treated at 1000 mg/kg bw.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	4 (1 M/3F)/10
2	5F	1000	0/5

- LD50: 1000-2000 mg/kg bw
- Signs of Toxicity - Local: General erythema, scales and/or scabs were noted in the treated skin areas of the animals treated with 2000 mg/kg bw. General erythema, erythema maculate and scales were noted in the treated skin areas of the animals treated with 1000 mg/kg bw.
- Signs of Toxicity - Systemic: Lethargy, abnormal posture, flat posture, hunched posture, uncoordinated movements, head drop, rales, shallow respiration, piloerection,

chromodacryorrhoea, hypersensitivity to touch, ptosis and/or hypothermia were noted in animals treated with 2000 mg/kg bw. By Day 7, the surviving animals had recovered from these effects. No clinical signs of systemic toxicity were noted in animals treated with 1000 mg/kg bw.

Effects in Organs: No abnormalities were found at macroscopic post mortem examination.

Remarks - Results: Changes in body weight gain were within the range expected for rats used in this type of study.

As female is generally the appropriate sex of test animals, LD50 is therefore considered to be 1000 - 2000 mg/kg bw.

CONCLUSION: The notified chemical is harmful via the dermal route.

TEST FACILITY: WIL (2015b)

B.3. Irritation – skin (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method
EPISKIN-SM™ Reconstructed Human Epidermis Model

Vehicle: None

Remarks - Method: In a preliminary test the test substance was shown not to directly reduce MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide].

The test substance (25 µL) was applied to the tissues in triplicate. Following exposure periods of 15 minutes (room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 42 hours.

Negative and positive controls were run in parallel with the test substance:
- Negative control: phosphate buffered saline (PBS)
- Positive control: 5% sodium dodecyl sulphate in PBS

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean viability (%)*	*SD of relative mean viability (%)*
Negative control	1.130	100	< 12%
Test substance	0.081	7	< 12%
Positive control	0.106	9	< 12%

OD = optical density; SD = standard deviation

Remarks - Results: The relative mean viability of the tissues treated with the test substance was 7% (predicted as irritating according to the criteria as below 50%).

The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

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

TEST FACILITY: WIL (2014a)

B.4. Irritation – eye (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals

Not Requiring Classification for Eye Irritation or Serious Eye Damage.

Vehicle: None

Remarks - Method: No significant protocol deviations. Physiological saline and 10% benzalkonium chloride in physiological saline were used as negative control and positive control respectively.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
*Negative control**	-1	0.000	-0.7
*Test substance**	13	0.051	14.1
*Positive control**	91	3.571	144.2

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

Remarks - Results: The test substance induced ocular irritation according to the opacity (12-15) and permeability (0.033-0.067) values. The corneas were slightly turbid with spots after the treatment. The in vitro irritancy score (IVIS) value was 14.1 (no prediction on the classification could be made according to the criteria as > 3 and ≤ 55).

The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

CONCLUSION: The notified chemical was considered irritating to the eye under the conditions of the test. However, no prediction on the classification was made.

TEST FACILITY: WIL (2015c)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE: Notified 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

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
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, there were no signs of systemic toxicity or irritation (the latter was indicated by < 25% increase in mean ear thickness) noted.

In the main study, there were no mortality 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 normal in size while the nodes of the animals in 100% concentration group were considered enlarged. No macroscopic abnormalities of the surrounding area were noted for any animals.

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

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

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

TEST FACILITY WIL (2015d)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

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	1000 (98 for males and females)	0/10
mid dose	5 per sex	3000 (296 for males and 300 for females)	0/10
high dose	5 per sex	10000 (1,011 for males and 944 for females)	0/10
high dose recovery	5 per sex	10000 (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 10000 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 3000 ppm showed incidentally slight higher body weight. These findings were not considered by the study authors to be toxicologically relevant due to the changes were slight and/or reversible.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Male and female animals treated with 10000 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 3000 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 10000 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 10000 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 10000 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 3000 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.

TEST FACILITY	WIL (2015e)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *E. coli*: WP$_2$*uvr*A
Metabolic Activation System	S9 mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test	Test 1 a) with/without metabolic activation: 5.4-5000 µg/plate Test 2 a) with/without metabolic activation: 5.4-512 µg/plate (TA1535, TA98 and TA100) b) with metabolic activation: 17-1600 µg/plate (TA1537) c) without metabolic activation: 5.4-512 µg/plate (TA1537) d) with/without metabolic activation: 52-5000 µg/plate (WP$_2$*uvr*A) Test 3 a) with metabolic activation: 512-1600 µg/plate (TA1535, TA98 and TA100)
Vehicle	Dimethyl sulfoxide
Remarks - Method	Test 1 was carried out at 5.4-5000 µg/mL. The dose selection for Test 2 was based on the toxicity observed in Test 1. Based on the results of Test 2, Test 3 was carried out at 512-1600 µg/mL using TA1535, TA98 and TA100 in the presence of metabolic activation. Positive controls: With metabolic activation: 2-aminoanthracene Without metabolic activation: sodium azide (TA1535); ICR-191 (TA1537); 2-nitrofluorene (TA98); methyl methanesulfonate (TA100); 4-nitroquinoline N-oxide (WP$_2$*uvr*A)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 164	> 5000	negative
Test 2	> 100	> 1600	negative
Present			
Test 1	> 164	> 5000	negative
Test 2	> 164	> 1600	negative
Test 3	≥ 512	> 1600	negative

Remarks - Results: No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

The positive and negative controls gave a satisfactory response 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 (2015f)

B.8. Genotoxicity – *in vitro*

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain: Human
Cell Type/Cell Line: Peripheral lymphocytes
Metabolic Activation System: S9 mix from Phenobarbital/β-naphthoflavone induced rat liver
Vehicle: Dimethyl sulfoxide
Remarks - Method: A dose range-finding study was carried out at 5.4 – 512 µg/mL. The dose selection for the main experiments was based on toxicity observed in the range-finding study.

Vehicle and positive controls (mitomycin C and cyclophosphamide) were run concurrently with the notified chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	5, 50, 100, 125, 150, 175, 200	3 h	24 h
Test 1A	100*, 125, 130, 135, 140*, 145, 150*, 155*, 160	3 h	24 h
Test 2	5*, 50, 75*, 100*, 125, 150	24 h	24 h
Test 2A	5*, 50*, 75*, 100, 125, 150	48 h	48 h
Present			
Test 1	5, 50, 100, 125, 150, 175, 200	3 h	24 h
Test 1A	100*, 125, 150, 155*, 160, 165, 170*, 175	3 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:* *Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 52	> 125	> 200	negative

Test 1A		> 150	> 160	negative
Test 2		> 75	> 150	negative
Test 2a		> 50	> 150	negative
Present				
Test 1	> 52	> 150	> 200	negative
Test 1A		> 165	> 175	negative

Remarks - Results

No statistically significant increases were noted in chromosome aberrations, either with or without metabolic activation.

The positive and vehicle controls gave satisfactory responses 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 (2015g)

Appendix C: Environmental Fate and Ecotoxicological Investigations

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge
Exposure Period	55 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Toxicity control was not conducted in parallel. However, this is not considered to affect the validity of the study because the test substance was determined not to have significantly adverse effects on bacterial respiration in another study provided.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	1	7	73
13	12	14	81
23	19	21	86
28	22	28	88
55	31	55	93

Remarks – Results	Toxicity control results are not available. All other validity criteria for the test are satisfied.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Givaudan (2013h)

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 C Inherent Biodegradability: Modified MITI test.
Inoculum	Activated sludge
Exposure Period	63 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	4	7	73
20	25	14	82
28	29	21	86
35	30	28	88
63	33	63	92

Remarks – Results	Toxicity control results are not available. All other validity criteria for the test are satisfied.
CONCLUSION	The notified chemical is not inherently biodegradable.
TEST FACILITY	Givaudan (2014e)

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	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	Acetone
Water Hardness	95 – 116 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography-flame ionisation detection (GC-FID)
Remarks – Method	The study was conducted according to the above guideline without significant deviation from the protocol. The test media were renewed every 24 hours.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
Control	-	7	0	0	0	0
0.625	0.31	7	0	0	0	0
1.25	0.65	7	0	0	0	0
2.5	1.2	7	0	0	0	0
5.0	2.5	7	0	0	0	4
10	4.2	7	7	7	7	7

LC50	3.2 mg/L at 96 hours (95% confidence limit: 2.7-3.9 mg/L)
NOEC	0.31 mg/L at 96 hours
Remarks – Results	All the validity criteria were satisfied. The measured concentrations of the test substances were not in the range of 80-120% of the nominal concentrations. Therefore, the results are based on mean measured concentrations.
CONCLUSION	The notified chemical is toxic to fish.
TEST FACILITY	Smithers Viscient (2014)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test – Semi-static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone
Water Hardness	Not reported
Analytical Monitoring	Gas chromatography-flame ionisation detection (GC-FID)
Remarks - Method	The study was conducted according to the above guideline without significant 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	0.49	20	0	0
1.8	0.85	20	0	0
3.2	1.6	20	0	0
5.6	2.7	20	1	3
10	4.6	20	8	20

EC50	3.4 mg/L at 48 hours (95% confidence limits: 3.0 - 3.7 mg/L)
NOEC	1.6 mg/L at 48 hours
Remarks - Results	All the validity criteria were satisfied. The measured concentrations of the test substances were less than 80% of the nominal concentrations. Therefore, the results are based on mean measured concentrations.

CONCLUSION The notified chemical is toxic to aquatic invertebrates.

TEST FACILITY Smithers Viscient (2015a)

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: Solvent control, 0.32, 1.0, 3.2, 10 and 32 mg/L Actual: N/A, 0.19, 0.66, 2.0, 7.2 and 23 mg/L
Auxiliary Solvent	Acetone
Water Hardness	Not reported
Analytical Monitoring	Gas chromatography-flame ionisation detection (GC-FID)
Remarks - Method	The study was conducted according to the above guideline without significant deviation from the protocol.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*72 mg/L*	*mg/L at 72 h*	*72 mg/L*
3.7	0.66	8.6	2.0
(95% confident limit: 2.8-4.5)		(95% confident limit: 5.8-10)	

Remarks - Results	All the validity criteria were satisfied. The measured concentrations of the test substances were less than 80% of the nominal concentrations. Therefore, the results are based on mean measured concentrations.

CONCLUSION The notified chemical is toxic to algae.

TEST FACILITY Smithers Viscient (2015b)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 100 mg/L Actual: Not determined

Remarks – Method	One limit test concentration of 100 mg/L was tested during the study. No significant deviations from the test guidelines above were reported.
RESULTS	
EC50	> 100 mg/L
Remarks – Results	The actual concentration of the test substance was not determined and the result was based on nominal concentration.
CONCLUSION	The notified chemical is not inhibitory to bacterial respiration.
TEST FACILITY	Givaudan (2014f)

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