File No.: LTD/1791

August 2020

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019 (the IC Act) and Industrial Chemicals (General) Rules 2019 (the IC Rules) by following the Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019 (the Transitional Act) and Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019 (the Transitional Rules)*. The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) 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 Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the AICIS website. For enquiries please contact AICIS at:

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Executive Director
AICIS

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SUMMARY

The following details will be published on our website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1791	Firmenich Pty Ltd	Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard Classification	*Hazard Statement*
Skin Sensitisation (Category 1B)	H317 - May cause an allergic skin reaction

Human Health Risk Assessment
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

When used at a maximum concentration of 0.5% in fine fragrances and household products (including air fresheners) and 0.1% in other cosmetics, the assessed chemical is not considered to pose an unreasonable risk to public health.

Environmental Risk Assessment
On the basis of the maximum import volume of one tonne per annum, the assessed chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The assessed chemical should be classified as follows:
  - Skin sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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

Health Surveillance

- As the assessed 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 sensitisation.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the assessed chemical during reformulation:
  - Enclosed/automated processes, where possible
  - Local exhaust ventilation and/or appropriate extraction systems, where possible

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

- 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 assessed chemical during reformulation:
  - Protective clothing
  - Impervious gloves
  - 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 SDS should be easily accessible to employees.

- If products and mixtures containing the assessed 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.

Storage

- The handling and storage of the assessed 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 assessed chemical should be handled by physical containment, collection and subsequent safe disposal.

Disposal

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

Regulatory Obligations

Specific Requirements to Provide Information
This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under Section 101 of the IC Act the applicant of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if:

- the importation volume exceeds one tonne per annum assessed chemical;
- the final use concentration of the assessed chemical exceeds 0.5% in fine fragrances and household products (including air fresheners), and 0.1% in other cosmetics;
- 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 human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

Safety Data Sheet
The SDS of the assessed chemical provided by the applicant was reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND APPLICATION DETAILS

APPLICANT(S)
Firmenich Pty Limited (ABN: 86 002 964 794)
73 Kenneth Road
BALGOWLAH NSW 2093

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

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
Data items and details taken to be protected information include: other names, analytical data, degree of purity, impurities, additives/adjuvants and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are varied for adsorption/desorption, dissociation constant, flammability, explosive properties and oxidising properties.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
EU (2004), USA (2005), Philippines (2006), Switzerland (2006), Japan (2007)

2. IDENTITY OF CHEMICAL

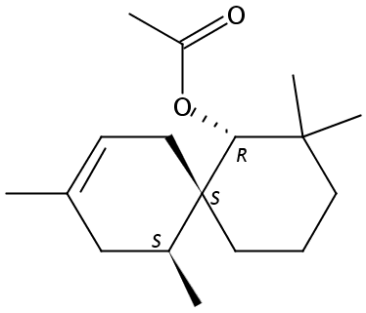
MARKETING NAME
Acetarolle

CAS NUMBER
678981-31-2

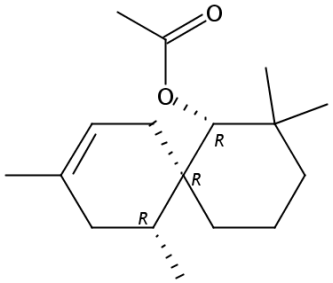
CHEMICAL NAME
Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate

MOLECULAR FORMULA
$C_{17}H_{28}O_2$

STRUCTURAL FORMULA
The assessed chemical consists of two diastereoisomers:



Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate, (1*R*,6*S*,11*S*)-*rel*- (CAS No. 678981-46-9)



Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate, (1*R*,6*R*,11*R*)-*rel*- (CAS No. 678981-47-0)

MOLECULAR WEIGHT
264.40 g/mol

ANALYTICAL DATA
Reference ^{1}H-NMR, ^{13}C-NMR, FTIR, GC-FID, GC-MS and UV-Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

Property	***Value***	***Data Source/Justification***
Freezing Point	< -20 °C	Measured
Boiling Point	297.5 °C at 97.6 kPa	Measured
Density	996 kg/m^3 at 20 °C	Measured
Vapour Pressure	5.3 × 10^{-4} kPa at 25 °C	Measured
Water Solubility	1.31 x 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Hydrolytically stable at 40 °C (pH 2-12, 5 days)	Measured
Partition Coefficient (n-octanol/water)	log Pow > 6.2 at 30 °C	Measured
Adsorption/Desorption	log K_{oc} = 4.29	Calculated using KOCWIN (v 2.0) (US EPA, 2012)
Dissociation Constant	Not determined	Contains no dissociable functionality
Flash Point	140 °C at 101.3 kPa	Measured
Flammability	Combustible liquid	Based on flashpoint
Autoignition Temperature	> 220 °C at 97.1 kPa	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties

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

Reactivity
The assessed 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 assessed 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 assessed chemical has a flash point of 140 ºC which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the assessed chemical may be considered as a Class C2 combustible liquid if the chemical has a fire point below the boiling point.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS
The assessed chemical will not be manufactured in Australia. The assessed chemical will be imported into Australia neat or as a component of fragrance formulations at ≤ 10% concentration, or in finished consumer products at ≤ 0.5% concentration.

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

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

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Firmenich Pty Ltd

TRANSPORTATION AND PACKAGING
The assessed chemical will be imported in neat form or as a component of fragrance formulations (at ≤ 10% concentration) in 5-180 kg closed lacquered drums. Within Australia, the drums will be transported from the port of entry by road to the applicant's warehouse facilities for storage and then distributed to industrial customers by road for reformulation. The assessed chemical may also be transported by road to the reformulation sites direct from the port of entry.

The assessed chemical may also be imported in finished consumer products at ≤ 0.5% concentration and transported by road to retail stores.

USE
The assessed chemical will be used as a fragrance ingredient at ≤ 0.5% in fine fragrances and household products (including air fresheners), and ≤ 0.1% in other cosmetics.

OPERATION DESCRIPTION
Reformulation of the assessed chemical or fragrance formulations (containing the assessed chemical at ≤ 10% concentration) into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes will involve blending operations that are highly automated and occur in fully enclosed/contained environments, followed by automated filling of the reformulated end-use products into containers of various sizes.

Consumers and professionals such as hairdressers, beauticians or cleaners will use the assessed chemical at ≤ 0.5% in fine fragrances and household products, and ≤ 0.1% in other cosmetics. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

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 storage workers	Not specified	Not specified
Mixer	4	2
Drum handling	4	2

Drum cleaning	4	2
Maintenance	4	2
Quality control	0.5	2
Packaging	4	2
Professional end users	Not specified	Not specified

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the assessed chemical in neat form, as a component of fragrance formulations at ≤ 10% concentration or in finished consumer products at ≤ 0.5% concentration, only in the unlikely event of accidental rupture of containers.

Reformulation workers

During reformulation, dermal, ocular and inhalation exposure of workers to the assessed chemical at ≤ 100% concentration may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The applicant states that exposure is expected to be minimised through the use of automated and/or enclosed processes, local exhaust ventilation and through the use of personal protective equipment (PPE) by workers such as protective clothing, eye protection, impervious gloves and respiratory protection.

Professional end users

Exposure to the assessed chemical in end-use products (at ≤ 0.5% concentration in fine fragrances and ≤ 0.1% concentration in other cosmetics) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers and workers in beauty salons). Exposure to the assessed chemical at ≤ 0.5% concentration in end-use products may also occur in professions where the services provided involve the use of household products in the cleaning industry. The principal route of exposure will be dermal, whilst ocular and inhalation exposure (e.g. spray products) 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 the products containing the assessed chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the assessed chemical through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure may also occur, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the assessed chemical may be used are shown in the following tables and these are based on information provided in various literature (Cadby *et al*., 2002; Loretz *et al.*, 2006; ACI, 2010; SCCS, 2012;). 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 assessed chemical for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Earnest, Jr, 2009; Rothe *et al*., 2011; Steiling *et al*., 2014). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%. A lifetime average female body weight (BW) of 70 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	0.10	1	0.1117
Face cream	1540	0.10	1	0.0220
Hand cream	2160	0.10	1	0.0309
Fine fragrances	750	0.50	1	0.0536
Deodorant (non–spray)	1500	0.10	1	0.0214
Shampoo	10460	0.10	0.01	0.0015
Conditioner	3920	0.10	0.01	0.0006
Shower gel	18670	0.10	0.01	0.0027
Hand wash soap	20000	0.10	0.01	0.0029
Hair styling products	4000	0.10	0.1	0.0057
Total				**0.2529**

C = maximum proposed concentration of assessed 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	0.5	0.95	10	0.0156
Fabric softener	90	0.5	0.95	10	0.0061
Total					**0.0217**

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

Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.5	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.5	1980	0.009	0.01	0.03	0.0011
All-purpose cleaner	1	0.5	1980	1	0.01	0.007	0.0099
Total							**0.0112**

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

Hairspray (Inhalation exposure):

Product type	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration zone 1 (min)	Exposure duration zone 2 (min)	Fraction inhaled (%)	Volume zone 1 (m^3)	Volume zone 2 (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.1	20	1	20	50	1	10	**0.0029**

C = maximum proposed concentration of assessed 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) × BW)]

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 assessed chemical at the maximum intended concentrations specified by the applicant in various product types. This would result in a combined internal dose of 0.2887 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, the combination of the conservative hair spray inhalation exposure assessment parameters used and the aggregate exposure from use of the dermally applied products (using a conservative 100% dermal absorption rate), are sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray cosmetic and household products containing it with low exposure (e.g. air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the assessed chemical, an analogue chemical, and its metabolite are summarised in the following table. For details of the studies on the assessed chemical, refer to Appendix B.

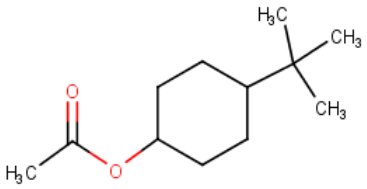
Endpoint	*Result and Assessment Conclusion*
Acute oral toxicity – rat	LD50 > 2000 mg/kg bw; low toxicity
Skin irritation – rabbit	slightly irritating
Eye irritation – rabbit	slightly irritating
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3 = 20.5%)
Skin sensitisation – HRIPT	no evidence of sensitisation at maximum tested concentration of 10%
Repeat dose oral toxicity – rat, 28 days*	NOAEL = 50 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic

Endpoint	*Result and Assessment Conclusion*
Reproductive and developmental toxicity – rat, 14 days**	NOAEL (maternal and developmental) = 160 mg/kg bw/day

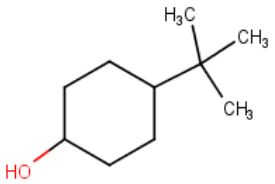
*From a study summary for a metabolite (4-*tert*-butylcyclohexanol, CAS No. 98-52-2) of an analogue chemical (Belsito *et al.*, 2008).
**From a study summary for an analogue chemical (4-*tert*-butylcyclohexyl acetate, CAS No. 32210-23-4) (Belsito *et al.*, 2008).

The assessed chemical and the analogue chemical, 4-*tert*-butylcyclohexyl acetate, are both considered as cyclic acetates. Both have similar molecular weights (264.4 g/mol and 198.3 g/mol, respectively) and share biologically relevant structural elements.

In humans, cyclic acetates are assumed to be rapidly hydrolysed to their corresponding alcohols and carboxylic acids. As such, 4-*tert*-butylcyclohexanol is considered a metabolite of 4-*tert*-butylcyclohexyl acetate (Belsito *et al.*, 2008).



4-*tert*-Butylcyclohexyl acetate



4-*tert*-Butylcyclohexanol

Toxicokinetics
No information on the toxicokinetics of the assessed chemical was provided. Given the low molecular weight of the assessed chemical (264.4 g/mol), absorption across biological membranes may occur. However dermal absorption may be limited based on its low water solubility (1.31 x 10-3 g/L at 20 °C) and high partition coefficient (log Pow > 6.2 at 30 °C).

Acute Toxicity
The assessed chemical was of low acute oral toxicity in rats. No acute dermal or inhalation toxicity data were provided for the assessed chemical.

Irritation and Sensitisation
In a skin irritation study in rabbits, slight erythema was observed in all test animals. However, all signs of irritation were resolved at the 48 hour observation.

In an eye irritation study in rabbits, mild to moderate conjunctival irritation was noted. However, all signs of irritation were resolved at the 72 hour observation.

The assessed chemical was found to be a weak skin sensitiser in a mouse local lymph node assay (LLNA), with an EC3 value of 20.5%.
The assessed chemical was not found to be a skin sensitiser in a human repeat insult patch test (HRIPT) when tested at 10% concentration.

Repeated Dose Toxicity
The Belsito *et al.* (2008) review article "A toxicologic and dermatologic assessment of cyclic acetates when used as fragrance ingredients" summarises safety data relating to assessing the risk associated with the use of some cyclic acetates as fragrance ingredients. The review contains a summary of a 28-day repeated dose oral toxicity study in rats conducted with 4-*tert*-butylcyclohexanol (CAS No. 98-52-2) at 0, 50, 150 and 300 mg/kg bw/day. This chemical is considered a metabolite of the analogue chemical in humans. The No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in males and females, based on clinical observations (convulsions, squatting position, straub tail and vocalisation) at higher tested doses (Belsito *et al.*, 2008).

Mutagenicity
The assessed chemical was non-mutagenic in a bacterial reverse mutation assay.

No genotoxicity test data was supplied.

Toxicity for Reproduction
No reproductive toxicity data was provided for the assessed chemical.

In a study summary for the analogue chemical, 4-*tert*-butylcyclohexyl acetate (CAS No. 32210-23-4), pregnant rats were dosed via oral gavage at 0, 40, 160, or 640 mg/kg bw/day on gestational days 7-20. The maternal NOAEL was established as 160 mg/kg bw/day. This was based on one rat in the high-dose group displaying adverse clinical observations (decreased motor activity, excess salivation, apparent dehydration; sacrificed on day 20) and all rats in the high-dose group presenting with sparse hair on the limbs, red perioral substance, reduced body-weight gains (entire treatment period) and significantly reduced absolute and relative feed consumption (entire treatment period) (Belsito et al., 2008).

The developmental NOAEL was established as 160 mg/kg bw/day. This was based on transient retardations in the offspring during foetal development. They included significant reductions in foetal body weight and associated significant increases in moderate dilation of the renal pelvis, delayed ossification of the caudal vertebrae, fore- and hind-limb phalanges and hind-limb metatarsals (Belsito *et al.,* 2008).

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

Hazard Classification	***Hazard Statement***
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided and available data, the assessed chemical is a weak skin sensitiser. It is also slightly irritating to the skin and eyes.

Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the assessed chemical at ≤ 100% concentration during reformulation. Given the assessed chemical is a skin sensitiser, caution should be exercised when handling the assessed chemical during reformulation processes.

Provided that control measures are in place to minimise worker exposure, including the use of enclosed, automated processes and PPE such as protective clothing, impervious gloves and respiratory protection (if inhalation exposure may occur), the risk to the health of workers during the handling of the assessed chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the assessed chemical at ≤ 0.5% concentration in fine fragrances and household products, and at ≤ 0.1% concentration in other cosmetics, similar to public use. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the assessed chemical is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2 below.

6.3.2. Public Health
Members of the public may experience repeated exposure to the assessed chemical through use of the assessed chemical at ≤ 0.5% in fine fragrances and household products, and ≤ 0.1% in other cosmetics.

Sensitisation
Based on the results of an LLNA, the assessed chemical is a weak skin sensitiser with an EC3 value of 20.5%. When tested in a HRIPT at 10% concentration, the assessed chemical was non-sensitising.

Using fine fragrances which contain the assessed chemical at ≤ 0.5% concentration as a worst-case example of leave-on cosmetic products containing the assessed chemical, the Consumer Exposure Level (CEL) is estimated

to be 18.75 μg/cm^2/day. Consideration of the HRIPT study details and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 49.80 μg/cm^2/day is estimated for the assessed chemical. In this instance, the factors employed in the estimation included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 100. The availability of additional information on the sensitisation potential of the assessed chemical (i.e., the LLNA study) was taken into account when determining the safety factors.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the assessed chemical in fine fragrances at ≤ 0.5% concentration (a worst-case example of leave-on cosmetic products containing the assessed chemical) is not considered to be unreasonable. Based on the lower expected exposure levels from other cosmetic and household products containing the assessed chemical, 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 assessed chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeated dose toxicity
The repeat dose toxicity potential was estimated based on the margin of exposure (MoE).

Using the worst case exposure scenario from use of multiple products, a total exposure of 0.2887 mg/kg bw/day (see Section 6.1.2) was derived. Using a NOAEL of 50 mg/kg bw/day for the assessed chemical (derived from a 28 day repeated dose oral toxicity study in rats with a metabolite of an analogue chemical), the margin of exposure (MoE) was estimated to be 173. 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 assessed chemical at ≤ 0.5% concentration in fine fragrances and household products (including air fresheners), and at ≤ 0.1% concentration in other cosmetics, 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 assessed chemical will be imported into Australia as a component of finished cosmetic and household products, or imported neat or as a component of fragrance oils for reformulation into cosmetic and household products. In general, reformulation processes are expected to involve automated blending operations in an enclosed environment, followed by automated filling of finished products into end-use containers. Wastewater generated from reformulation equipment cleaning is expected to be reused for new purposes. Empty import containers will be either recycled or disposed of through an approved waste management facility. Accidental spills or leaks of the assessed chemical is expected to be collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE
The majority of the assessed chemical is expected to be released to sewers across Australia as a result of its use in cosmetic and household products, which are washed off the hair and skin of consumers as well as from cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL
Residues of the assessed chemical in empty end-use containers are either recycled or disposed of to landfill, in accordance with local government regulations. The applicant estimates that 3% of the end use products (containing the assessed chemical at ≤ 0.5% concentration) will remain in empty end use containers.

7.1.2. Environmental Fate
Following its use in cosmetic and household products, the majority of the assessed chemical will enter the sewers and be treated at sewage treatment plants (STPs) before potential release to surface waters nationwide. A proportion of the assessed chemical may volatilise to air. The half-life of the assessed chemical in air is calculated to be 1.26 hours reaction with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). Therefore, the assessed chemical is not expected to persist in the air compartment.

A ready biodegradation test conducted on the assessed chemical indicates that it is not readily biodegradable (9% degradation over 28 days). However, the ready biodegradability tests (OECD 301 series A-F) are stringent screening tests and chemicals which pass the thresholds will almost invariably biodegrade rapidly and completely. Failure to pass these requirements of these studies does not automatically mean that a chemical is unlikely to biodegrade in the environment. The main reasons for this, are that the detection methods are indirect and do not provide information on any intermediate breakdown products and the inoculum only represents a tiny fraction of the organisms which may degrade chemicals in the environment (Boethling & Mackay, 2000). Although the assessed chemical is not readily biodegradable, it contains an ester functionality which has a common microbial degradation pathway (*ibid*). The results of the ready biodegradation study supports this premise as degradation was initially slow with a rapid increase before termination. Therefore the assessed chemical is unlikely to be persistent in the environment. For details of the biodegradation study, refer to Appendix C.

The assessed chemical is expected to highly sorb to sludge at STPs based on its low water solubility and high partition coefficient (log Pow > 6.2). Therefore, the assessed chemical is expected to be removed effectively at STPs through biodegradation and adsorption to sludge, and only a small portion of the assessed chemical may be released to surface waters. A proportion of the assessed chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation or disposed of to landfill. The assessed chemical as residues in landfill and soils is expected to have very low mobility based on its soil adsorption coefficient (log Koc = 4.29).

The assessed chemical has bioaccumulation potential based on its octanol-water partition coefficient value (log Pow > 6.2) and lack of ready biodegradability. However, overall the assessed chemical is not expected to be persistent in the environment and is therefore unlikely to bioaccumulate. In the aquatic and soil compartments, the assessed chemical is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the assessed chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the assessed chemical into sewer systems nationwide over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes based on the properties of the assessed chemical has not been considered for this scenario, and therefore no removal of the assessed chemical during sewage treatment processes is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	**Mitigation**
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 1,000 L/m^2/year (10 ML/ha/year). The assessed chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.75 µg/kg.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was not calculated as no ecotoxicity data were submitted.

7.3. Environmental Risk Assessment

The Risk Quotient (PEC/PNEC) was not calculated as no ecotoxicity data were submitted. The assessed chemical undergoes inherent degradation and is therefore unlikely to be persistent in the environment. On the basis of the maximum import volume of one tonne per annum, the assessed chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < - 20 °C

Method	OECD TG 102 Melting Point/Melting Range (1995) Commission Directive 92/69/EEC A.1 Melting/Freezing Temperature (1992)
Remarks	Freezing temperature measured in a dry ice/isopropanol bath
Test Facility	Firmenich (2003a)

Boiling Point 297.5 °C at 97.6 kPa

Method	OECD TG 103 Boiling Point (1995) Commission Directive 92/69/EEC A.2 Boiling Temperature (1992)
Remarks	Determined by Siwoloboff method
Test Facility	Firmenich (2003a)

Density 996 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids (1995) Commission Directive 92/69/EEC A.3 Relative Density (1992)
Remarks	Determined by oscillating density meter
Test Facility	Firmenich (2003a)

Vapour Pressure 5.3×10^{-4} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure (1995)
Remarks	Determined using dynamic measurement
Test Facility	Firmenich (2003b)

Water Solubility 1.31×10^{-3} g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method. The concentration of the test substance was analysed by High Performance Liquid Chromatography (HPLC).
Test Facility	SafePharm (2003a)

Hydrolysis as a Function of pH Hydrolytically stable at 40 °C

Method	Internal method: the test substance was dissolved in pH buffers containing surfactant and stored at 40 °C. Small aliquots of the test solution were extracted with an organic solvent containing a hydrocarbon standard at 0, 0.25, 1, 2, 4, 7, 15, 21 and 28 days throughout the test. The extracts were analysed by gas chromatography-flame ionisation detector (GC-FID).
Remarks	The test substance was found hydrolytically stable at pH 2, 5, 7, 8.5, 12 and 40 °C.
Test Facility	Firmenich (2014)

Partition Coefficient (n-octanol/water) log Pow = > 6.2 at 30 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method; the column temperature was 30 °C.
Test Facility	SafePharm (2003a)

Flash Point 140 °C at 101.3 kPa

Method	Commission Directive 92/69/EEC A.9 Flash Point (1992)
Remarks	Closed cup method
Test Facility	Firmenich (2003a)

Autoignition Temperature > 220 °C at 97.1 kPa

Method	Similar to EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Test conducted up to 220 °C
Test Facility	Firmenich (2003c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001)
Species/Strain	Rat/ Sprague-Dawley CD
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	There were no unscheduled deaths during the study. No clinical signs of systemic toxicity were observed.
Effects in Organs	No abnormalities were recorded at necroscopy.
Remarks – Results	All animals showed expected body weight gains over the study period.
CONCLUSION	The assessed chemical is of low acute toxicity via the oral route.
TEST FACILITY	SafePharm (2003b)

B.2. Skin Irritation – Rabbit

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (1992) EC Directive 92/69/EEC Method B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 male
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations. After a single 4-hour application on the intact back skin of 3 male rabbits, test sites were assessed for dermal irritation at 1, 24, 48 and 72 hours.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.3	0.3	0.3	1	< 48 h	0
Oedema	0	0	0	0	-	0

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

Remarks – Results	Slight erythema was observed in all test animals at the 1 and 24 hour observations. All observed effects were reversed to normal by 48 hours.
CONCLUSION	The assessed chemical is slightly irritating to the skin.

TEST FACILITY SafePharm (2003c)

B.3. Eye Irritation – Rabbit

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion (2002)
EC Directive 92/69/EEC Method B.5 Acute Toxicity (Eye Irritation)

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 male
Observation Period	72 hours
Remarks – Method	No significant protocol deviations. Test sites were assessed for ocular damage/irritation at 1, 24, 48 and 72 hours after administration of the test chemical.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: Redness	0.3	0	0.3	1	< 48 h	0
Conjunctiva: Chemosis	0	0	0	0	< 24 h	0
Conjunctiva: Discharge	0.3	0	0	1	< 48 h	0
Corneal Opacity	0	0	0	0	-	0
Iridial Inflammation	0	0	0	0	-	0

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

Remarks – Results Minimal to moderate conjunctival irritation was noted in all animals 1 hour after treatment. Minimal conjunctival irritation was observed in two animals at the 24 hour observation. All observed effects were reversed to normal by 48 hours. No corneal or iridial effects were observed.

CONCLUSION The assessed chemical is slightly irritating to the eye.

TEST FACILITY SafePharm (2003d)

B.4. Skin Sensitisation – LLNA

TEST SUBSTANCE Assessed chemical

METHOD In-house protocol (similar to OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010))

Species/Strain	Mouse/CBA/J
Vehicle	Acetone:olive oil (4:1)
Preliminary study	No
Positive control	Isoeugenol (conducted in parallel with the test substance).
Remarks – Method	No significant protocol deviations. No pre-screen test to determine the maximum appropriate test substance concentration was reported.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (mean DPM/mouse ± SD)*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	8F	36.7 ± 15.7	
1	5F	29.2 ± 3.6	0.8
5	5F	36.7 ± 6.0	1.0

10	5F	46.3 ± 10.6	1.3
20	5F	118.7 ± 48.4	3.2
40	5F	266.6 ± 101.2	7.3
Positive Control			
0.5	5F	55.7 ± 16.3	1.5
1.0	5F	85.0 ± 33.4	2.3
5.0	5F	333.9 ± 125.0	9.1

EC3 20.5%

Remarks – Results No irritation, mortalities, signs of systemic toxicity or effects on body weight were noted in the test animals.

The test substance elicited stimulation indices (SI) ≥ 3 at the 20% and 40% concentrations, although only the 40% concentration was statistically significant.

The EC potency value for the test substance was determined to be 5,125 μg/cm^2.

The authors of this study noted that mean ear thickness between days 1 and 3 did not increase by 10% or more in any tested animals, and thus primary irritation was not considered a contributing factor in the lymph node proliferation observed in the study.

The calculated EC3 and potency value for the positive control (1.32% and 330 μg/cm^2, respectively) were consistent with previously reported results, thereby confirming the reliability of the test system.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the assessed chemical.

TEST FACILITY BRT (2004)

B.5. Skin Sensitisation – Human Volunteers

TEST SUBSTANCE Assessed chemical (10% in vehicle)

METHOD Human repeated insult patch test (HRIPT)

Study Design A pilot study was conducted prior to the main study to determine the feasibility of testing the test substance on a larger study population by evaluating the ability of the test substance to sensitise the skin of normal subjects.

The pilot study and the main study both consisted of three phases:

- Induction phase: 9 × 24-hour applications (0.2 mL), grading of responses at 48- or 72-hour intervals over a 3-week period
- Rest phase: 10–15 days
- Challenge phase: 1 × 24-hour application (0.2 mL) on a naïve site, grading of responses at 48 or 72 hours post patch removal.

Rechallenge was not conducted.

Study Groups Pilot Study: 16 F, 2 M; age range 29 – 73 years
Main Study: 91 F, 23 M; age range 18 – 70 years

Vehicle Diethyl phthalate

Remarks – Method Occluded and semi-occluded. The test substance was spread on a 2 cm × 2 cm patch.

RESULTS

Remarks – Results	Pilot study: 17/18 subjects completed the study (1 subject voluntarily withdrew after the first induction application, before grading could be conducted). No adverse reactions were recorded during the challenge phase. In the pilot study challenge phase, 1/17 subjects exhibited a minimal or doubtful response at 48 and 72 hours. Main study: 100/114 subjects completed the study. Ten applicants were discontinued for failure to keep to the scheduled visits (3-6 induction observations recorded) and four voluntarily withdrew (following the first and second induction readings). A minimal or doubtful response was noted for 1 subject at the first induction grading. No responses were noted during the challenge phase.
CONCLUSION	The assessed chemical (at 10% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (2004)

B.6. Genotoxicity – Bacteria

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure (48-hour incubation at 37 °C)
Species/Strain	*Salmonella typhimurium*: TA1535, TA100, TA102, TA1537, TA98
Metabolic Activation System	S9 fractions from phenobarbitone/β-naphthoflavone induced rat livers
Concentration Range in Main Test	a) With metabolic activation: 50–5000 µg/plate b) Without metabolic activation: 50–5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks – Method	No deviations from the test guideline Preliminary toxicity test: TA100 exposed to ten concentrations of the test substance ranging 0.15–5000 µg/plate, with and without metabolic activation, to select appropriate dose levels for the main study. Test 1 and 2 of the main study: each strain exposed to five concentrations of test substance, with and without metabolic activation. Vehicle, negative and positive controls were conducted in parallel with the test substance. Positive controls: i) with metabolic activation: 2-aminoanthracene (TA100, TA1535, TA1537), 1,8-dihydroxyanthraquinone (TA102), and benzo(a)pyrene (TA98) ii) without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535), 9-aminoacridine (TA1537), mitomycin C (TA102) and 4-nitroquinoline-1-oxide (TA98)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test (TA100)	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	> 5000	5000	negative
Test 2		> 5000	5000	negative
Present				
Test 1	> 5000	> 5000	5000	negative
Test 2		> 5000	5000	negative

Remarks – Results

In the preliminary toxicity study, the test substance was non-toxic to the TA100 strain at up to 5000 µg/plate, with or without metabolic activation.

The authors of this study noted that an oily precipitate (noted under an inverted microscope only) at 5000 µg/plate would not prevent the scoring of revertant colonies.

No reduction in the growth of the bacterial background was visible at any tested dose levels, with or without metabolic activation.

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

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

CONCLUSION

The assessed chemical was non-mutagenic to bacteria under the conditions of the test.

TEST FACILITY

SafePharm (2003e)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test.
Inoculum	Activated sludge from a sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Carbon Dioxide ($ThCO_2$)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The test substance was poorly soluble in water and therefore it was adsorbed onto an inert support (glass fibre filter paper) prior to dispersion in the test medium in order to increase the surface area to the test organisms. The positive control was sodium benzoate. A toxicity control comprising of the test material adsorbed onto filter paper plus sodium benzoate, was also run.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	0	6	67
14	3	14	78
22	0	22	74
28	9	28	82

Remarks - Results	All validity criteria for the test were satisfied. The toxicity control attained 28% degradation on day 14 thereby confirming that the assessed chemical was not toxic to the sewage treatment micro-organisms used in the study. The total CO_2 evolution in the control vessels on day 28 was 25.48 mg/L. The difference between values for CO_2 production at the end of the test for the replicate vessels was < 20%. The test material attained 9% degradation after 28 days and, therefore, cannot be considered as readily biodegradable under the conditions of OECD Guideline 301B.
CONCLUSION	The assessed chemical is not readily biodegradable
TEST FACILITY	SafePharm (2003f)

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