File No.: LTD/2143

August 2020

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

5-Octen-4-ol, 3,5-dimethyl-, (5*E*)-

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/2143	Firmenich Limited	5-Octen-4-ol, 3,5-dimethyl-, (5*E*)-	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*
Flammable liquid (Category 4)	H227 – Combustible liquid
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Eye irritation (Category 2B)	H320 – Causes eye irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 2	H401 - Toxic to aquatic life

Human Health Risk Assessment
Under the conditions of the occupational settings described, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio, 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:
  - Flammable liquid (Category 4): H227 – Combustible liquid
  - Acute toxicity (Category 4): H302 – Harmful if swallowed
  - Eye irritation (Category 2B): H320 – Causes eye irritation
  - 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.

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:
  - Impervious gloves
  - Safety glasses
  - Protective clothing
  - 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.

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.

Transport and Packaging

- Due to the flammability of the assessed chemical, introducers of the chemical should consider their obligations under *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG code) (NTC, 2018).

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 containment, physical 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 1.21% in fine fragrances, 0.61% in deodorants, 0.2% in other cosmetic products or household cleaning products, 10% in electrical air fresheners or 1% in aerosol, spray and candle air fresheners;
- 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; and
- 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
Firmenich 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: specific other names, analytical data, degree of purity, impurities and additives/adjuvants.

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

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
EU

2. IDENTITY OF CHEMICAL

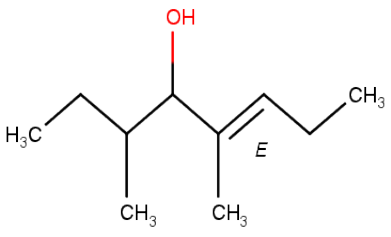
MARKETING NAME(S)
(5*E*)-3,5-Dimethyl-oct-5-en-4-ol

CAS NUMBER
2209852-19-5

CHEMICAL NAME
5-Octen-4-ol, 3,5-dimethyl-, (5*E*)-

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

STRUCTURAL FORMULA



MOLECULAR WEIGHT
156.27 g/mol

ANALYTICAL DATA
Reference NMR, IR, 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 to pale yellow liquid

Property	*Value*	*Data Source/Justification*
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	201.4 °C at 102 kPa	Measured
Density	850 kg/m^3 at 20 °C	Measured
Vapour Pressure	11.7 × 10^{-3} kPa at 20 °C 18.5 × 10^{-3} kPa at 25 °C	Measured
Water Solubility	0.429 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Unstable at pH 2 and 5, and stable at pH 7, 8.5 and 12 at 40°C	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.2 at 22 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.56 to 2.62 at 30 °C	Measured
Dissociation Constant	Not determined	Contains no dissociable functionality
Flash Point	84 ± 2 °C at 101.3 kPa	Measured
Flammability	Not measured	Classified as combustible liquid based on flash point
Autoignition Temperature	258 °C	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 oxidative 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 recommended for physical hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard Classification	*Hazard Statement*
Flammable Liquid (Category 4)	H227 – Combustible liquid

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. It will be imported into Australia either in the neat form or as a component in fragrance formulations (at ≤ 20% concentration) or finished consumer products (at ≤ 10% 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

TRANSPORTATION AND PACKAGING
The imported assessed chemical or products containing it will be transported by road via truck to the applicant's warehouse or customers' facilities for storage or reformulation. Fragrance formulations containing the assessed chemical will be imported and distributed in tightly closed lacquered drums of varying sizes: 180, 100, 50, 25, 10 or 5 kg. End-use products will be packaged in containers suitable for retail sale.

USE
The assessed chemical will be used as a fragrance ingredient in a variety of cosmetic and household products at final use concentrations of ≤ 1.21% in fine fragrances, ≤ 0.61% in deodorants, ≤ 0.2% in other cosmetic products and household cleaning products, ≤ 10% in electrical air fresheners and ≤ 1% in aerosol, spray and candle air fresheners.

OPERATION DESCRIPTION
The reformulation procedures for incorporating the assessed chemical into end-use products will likely vary depending on the nature of the cosmetic and personal care/household cleaning products formulated. This may involve both automated and manual processes including transferring and blending the assessed chemical with other formulations. However, a typical blending operation will be highly automated and occur in a fully enclosed/contained environment, followed by automated filling using sealed delivery systems into containers of various sizes.

The end-use products containing the assessed chemical may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. 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 warehouse	unknown	unknown
Mixing	4	2
Drum handling	4	2
Drum cleaning	4	2
Maintenance	4	2
Quality control	0.5	1
Packaging	4	2
Professional end users	not specified	not specified

EXPOSURE DETAILS

Transport and storage
Transport, storage and warehouse workers may come into contact with the assessed chemical in neat form or as a component of the imported preparations, only in the event of accidental rupture of containers.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the assessed chemical (at up to 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 mechanical ventilation and/or enclosed systems, and through the use of personal protective equipment (PPE) such as protective clothing, goggles, impervious gloves and respiratory protection if required.

End use
Exposure to the assessed chemical in end-use products (at ≤ 10% concentration) may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hairdressers and workers in beauty salons), or the use of household products in the cleaning industry. Such professionals may use 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 at ≤ 10% concentration through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if the 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 literatures (SCCS, 2012; Cadby *et al*., 2002; ACI, 2010; Loretz *et al*., 2006). For the purposes of 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 (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 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	0.2	1	0.2234
Face cream	1540	0.2	1	0.0440
Hand cream	2160	0.2	1	0.0617
Fine fragrances	750	1.21	1	0.1296
Deodorant	1500	0.61	1	0.1307
Shampoo	10460	0.2	0.01	0.0030
Conditioner	3920	0.2	0.01	0.0011
Shower gel	18670	0.2	0.01	0.0053
Hand soap	20000	0.2	0.01	0.0057
Hair styling products	4000	0.2	0.1	0.0114
Total				**0.6161**

C = maximum intended 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	0.2	0.95	10	0.0062
Fabric softener	90	0.2	0.95	10	0.0024
Total					**0.0087**

C = maximum intended 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	0.2	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.2	1980	0.009	0.01	0.03	0.0005
All-purpose cleaner	1	0.2	1980	1	0.01	0.007	0.0040
Total							**0.0045**

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

Hair spray (inhalation exposure)

Product type	**Amount**	**C**	**Inhalation Rate**	**Exposure duration (Zone 1)**	**Exposure Duration (Zone 2)**	**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	0.2	20	1	20	50	1	10	**0.0059**

C = maximum intended 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) × body weight)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemical at the maximum intended concentrations specified by the applicant in various product types. This would result in a combined internal dose of 0.6351 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 are summarised in the following table. For details of the studies, refer to Appendix B.

Endpoint	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LD50 > 300 and < 2,000 mg/kg bw; harmful
Skin irritation – *in vitro* EpiSkin™ reconstructed human epidermis test	not classified as a skin irritant
Eye irritation – *in vitro* isolated chicken eye test	no prediction can be made
Eye irritation – rabbit	irritating
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3 = 64.3%)
Repeat dose oral (diet) toxicity – rat, 14 days	dose range determined
Combined repeated dose oral (diet) toxicity study with the reproduction/developmental toxicity screening test – rat, up to 56 days	systemic NOAEL = 2,500 ppm for males and 12,000 ppm for females (equivalent to 146 and 806 mg/kg bw/day, respectively)*; reproductive/developmental NOAEL = 12,000 ppm (equivalent to 838 mg/kg bw/day during gestation and 1763 mg/kg bw/day during lactation)*
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test	non genotoxic

*Established by study authors

Toxicokinetics, Metabolism and Distribution

Given the low molecular weight (156.27 g/mol) and partition coefficient (log Pow = 3.2 at 22 °C) of the assessed chemical, absorption across biological membranes may occur.

Acute Toxicity

The assessed chemical is harmful via the oral route based on a study conducted in rats in which the LD50 was determined to be between 300 to 2,000 mg/kg bw.

No dermal toxicity or inhalation toxicity studies were submitted. Inhalation of vapour is not expected as the assessed chemical has low vapour pressure.

Irritation

In an *in vitro* study using the EpiSkin™ reconstructed human epidermis test model, the assessed chemical was determined not to require classification for skin irritation under the GHS according to the test guideline.

Based on the results in an *in vitro* isolated chicken eye (ICE) test, no prediction can be made for eye irritation of the assessed chemical. The assessed chemical was found to be irritating to eyes in a study conducted in rabbits, warranting hazard classification (Cat 2B).

Sensitisation
The assessed chemical was determined to be a weak skin sensitiser in a mouse local lymph node assay (LLNA) with stimulation indices of 1.6, 2.8 and 3.5 at 25%, 50% and 100%, respectively. The EC3 value (i.e. the estimated concentration of a test substance needed to produce a stimulation index of three) was calculated to be 64.3% and the assessed chemical warrants classification as a weak skin sensitiser (Cat 1B).

Repeated Dose Toxicity
A combined repeated dose oral (diet) toxicity study with the reproduction/developmental toxicity screening test was conducted in rats with the assessed chemical at dose levels of 0, 2500, 6000 and 12000 ppm. The dose selection of this study was based on the results of a previous 14-day dose range finding study. In this combined repeated dose toxicity with reproduction/developmental screening study, test substance-related adverse histopathological changes (nephropathy) were noted in the kidneys of males treated at 6000 or 12000 ppm, with associated increases in body weight adjusted male kidney weights, dose-related increases in group mean urea concentration, high total protein concentration in males treated at 12000 ppm, dose-related increases in total protein output and total glucose output in the urine, increases in protein concentration and glucose concentration in the urine of males treated at 12000 ppm, a dose-related decrease in the total creatinine output and a non-dose-related decrease in creatinine concentration in the urine. Based on these findings, the No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established by the study authors as 2,500 ppm (equivalent to 146 mg/kg bw/day) for males and 12,000 ppm (equivalent to 806 mg/kg bw/day) for females.

The NOAEL for reproductive/developmental toxicity was established by the study authors as 12,000 ppm (equivalent to 838 during mg/kg bw/day during gestation and 1763 mg/kg bw/day during lactation) based on there were no test substance-related reproductive/developmental effects up to the highest dose tested.

Mutagenicity/Genotoxicity
The assessed chemical was tested negative in a bacterial reverse mutation assay and in an *in vitro* mammalian cell micronucleus test in human lymphocytes.

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***
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Eye irritation (Category 2B)	H320 – Causes eye irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided, the assessed chemical is a weak skin sensitiser and an eye irritant. No inhalation toxicity data were provided. Effects following repeated exposure at high doses could not be ruled out based on the information available on the assessed chemical.

Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the assessed chemical up to 100% concentration during reformulation. Given the assessed chemical is a skin sensitiser and an eye irritant, control measures to prevent worker exposure are required 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 impervious gloves, safety glasses, protective clothing 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 ≤ 10% concentration, 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 the use of cosmetic and household products containing the assessed chemical at ≤ 10% concentration.

Sensitisation
Based on the results of an LLNA, the assessed chemical is a skin sensitiser with an EC3 value of 64.3%. Using fine fragrance as a worst-case example of leave-on cosmetic products that may contain the assessed chemical at ≤ 1.21% concentration, the Consumer Exposure Level (CEL) is estimated to be 45.38 μg/cm^2/day. Consideration of available information and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 45.55 μg/cm^2/day is estimated for the assessed chemical. 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 the assessed chemical in fine fragrances at ≤ 1.21% concentration (a worst-case example of leave-on cosmetic products) is not considered to be unreasonable. Based on lower expected exposure level from other cosmetic 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 assessed chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeated use
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the assessed chemical using the worst case exposure scenario from use of multiple products by an individual with total exposure of 0.6351 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 146 mg/kg bw/day for the assessed chemical (derived from a combined repeated dose oral toxicity study with the reproduction/developmental toxicity screening test in rats on the assessed chemical), the margin of exposure (MoE) was estimated to be 230. 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 ≤ 1.21% in fine fragrances, ≤ 0.61% in deodorants, ≤ 0.2% in other cosmetic products and household cleaning products, ≤ 10% in electrical air fresheners and ≤ 1% in aerosol, spray and candle air fresheners 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 operation 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 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 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, estimated by the applicant to account for up to 3% of the total import volume, are either recycled or disposed of to landfill, in accordance with local government regulations.

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 (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 readily biodegradable (63% degradation over 28 days). For details of the biodegradation study, refer to Appendix C. The assessed chemical is expected to be removed effectively at STPs through biodegradation, 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 moderate mobility based on its soil adsorption coefficients (log K_{oc} = 2.56 and 2.62).

The assessed chemical is unlikely to bioaccumulate based on its ready biodegradability and octanol-water partition coefficient (log Pow = 3.2). 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. Accumulation between applications is not expected, as the assessed chemical readily degrades.

7.2. Environmental Effects Assessment
The results from ecotoxicological investigations conducted on the assessed 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 = 10.4 mg/L	Harmful to fish

Daphnia Toxicity	48 h EC50 = 18.6 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h ErC50 = 10 mg/L	Toxic to algae
Inhibition of Bacterial Respiration	3 h IC50 = 143 mg/L	Not inhibitory to bacterial respiration

Based on the ecotoxicological endpoints for the assessed chemical, it is expected to be toxic to algae and harmful to fish and daphnia on an acute basis. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the assessed chemical is formally classified as "Acute Category 2; Toxic to aquatic life".

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for Algae. A safety factor of 100 was used given acute endpoints for three tropic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
ErC50 (Algae, 72 h)	10	mg/L
Assessment Factor	100	
PNEC:	100	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	100	**< 0.01**
Q - Ocean	0.056	100	**< 0.01**

The risk quotient for discharge of treated effluents containing the assessed chemical to the aquatic environment indicates that the assessed chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The assessed chemical is readily biodegradable and expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio the assessed chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -20 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined using crystallizing point method
Test Facility	Envigo (2018a)

Boiling Point 201.4 °C at 102 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Determined using differential scanning calorimetry
Test Facility	Envigo (2018a)

Density 850 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Determined using a glass pycnometer
Test Facility	Envigo (2018a)

Vapour Pressure 18.5×10^{-3} kPa at 25 °C
11.7×10^{-3} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Determined using gas saturation method
Test Facility	Envigo (2018b)

Water Solubility 0.429 g/L at 20 ± 0.5 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	NOACK (2018a)

Hydrolysis as a Function of pH Unstable at pH 2 and 5, and stable at pH 7, 8.5 and 12 at 40°C

Method	Internal method: the test chemical 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	At pH 2 the assessed chemical degraded rapidly, with less than 20% detected after less than one day. Degradation continued and 15% remained at day 5 and less than 10 % at day 28. At pH 5 the degradation occurred steadily with 85% remaining after 5 days and approximately 55% after 28 days. No degradation was observed at any other pH.
Test Facility	Firmenich (2019)

Partition Coefficient (n-octanol/water) log Pow = 3.2 at 22 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC method
Test Facility	NOACK (2018b)

Adsorption/Desorption log Koc = 2.56 to 2.62 at 30 °C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
Remarks	The HPLC method was considered to be suitable for the purpose of the study since it showed two main peaks with well-defined and reproducible retention times. The peaks represent the two stereoisomers of the assessed chemical.
Test Facility	Envigo (2019a)

Flash Point 84.2 ± 2 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Determined using closed cup equilibrium method
Test Facility	Envigo (2018c)

Autoignition Temperature 258 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Determined using flask heater procedure
Test Facility	Envigo (2018c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat, Fixed Dose

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method
Species/Strain	Rat/Wistar (RccHanTM:WIST)
Vehicle	Arachis oil BP
Remarks – Method	No significant protocol deviations

RESULTS

Sighting Study

Dose (mg/kg bw)	*Administered*	*Evident Toxicity*	*Mortality*
2000	gavage	no	0/1
300	gavage	no	0/1

Signs of Toxicity	Hunched posture was observed in the 2000 mg/kg bw dose group at the 1-hour observation and appeared to resolve at the 2-hour observation. No signs of systemic toxicity were noted in the 300 mg/kg bw dose group.
Effects in Organs	No abnormalities were noted at necropsy.

Main Study

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	4 F	2000	2/4
2	4 F	300	0/4

LD50	> 300 and < 2,000 mg/kg bw
Signs of Toxicity	In the 2000 mg/kg bw dose group, 2/4 animals showed a loss of righting reflex, lethargy, laboured respiration and decreased respiratory rate at the 1-hour observation and were found dead at the 2-hour observation. Hunched posture was observed in the remaining animals of this group with the addition of ataxia in 1 animal at the 1-hour observation, which persisted to the 4-hour observation. The remaining animals appeared normal at the Day 1 observation until the end of the observation period on Day 14. No signs of systemic toxicity were noted in the 300 mg/kg bw dose group.
Effects in Organs	In the 2000 mg/kg bw dose group, the 2 animals that died showed patchy pallor in the liver and the animal that displayed hunch posture and ataxia showed ulceration of the non-glandular region of the stomach at necropsy. The remaining animals showed no abnormalities at necropsy. There were no abnormalities in animals of the 300 mg/kg bw dose group at necropsy.
Remarks – Results	Surviving animals showed expected body weight gain over the observation period.

CONCLUSION	The assessed chemical is harmful via the oral route.
TEST FACILITY	Envigo (2018d)

B.2. Skin Irritation – *In Vitro* EpiSkin™ Reconstructed Human Epidermis Model

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method

	EpiSkin™ Reconstructed Human Epidermis Model
Vehicle	None
Remarks – Method	No significant protocol deviations. In a pre-test, the test substance was shown not to directly reduce MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Positive and negative controls were run in parallel with the test substance: - Negative control: Dulbecco's phosphate buffered saline (DPBS) - Positive control: 5% (v/v) sodium dodecyl sulfate (SDS)

RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	0.736	100	11.5
Test substance	0.605	82.2	1.5
Positive control	0.067	9.1	4.9

OD = optical density; SD = standard deviation

Remarks – Results	The positive and negative controls gave satisfactory responses confirming the validity of the test system and quality of the tissues.
CONCLUSION	Based on the mean tissue viability of > 50%, the assessed chemical is not classified as a skin irritant according to the GHS criteria.
TEST FACILITY	Envigo (2018e)

B.3. Eye Irritation – *In Vitro* Isolated Chicken Eye Test

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 438 Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (2017)
Vehicle	None
Remarks – Method	No significant protocol deviations. Negative control (0.9% sodium chloride) and positive control (5% benzalkonium chloride in distilled water) were run concurrently with the test substance.

RESULTS

Test Material	*Maximal mean score for corneal opacity (ICE Class)*	*Mean score of Fluorescein retention (ICE Class)*	*Maximal corneal swelling (ICE Class)*
Negative control	0.5 (I)	0.5 (I)	2.78 (I)
Test substance	2.3 (III)	2.0 (III)	17.65 (III)
Positive control	4.0 (IV)	3.0 (IV)	41.94 (IV)

Remarks – Results	Translucent corneal opacity and slight obscurity of the iris was observed in 2/3 eyes treated with the test substance. Severe corneal opacity, obscurity of the iris and pupil was observed in the 1/3 eyes. Some degree of fluorescein staining was noted in test substance treated eyes. No morphological effects were noted in test substance treated eyes. Based on the combined scores (3 × Class III) of the test substance, no prediction for eye irritation can be made according to the test guideline. The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

CONCLUSION	No prediction for eye irritation can be made based on the results of this study.
TEST FACILITY	Envigo (2018f)

B.4. Eye Irritation – Rabbit

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 F
Observation Period	7 days
Remarks – Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Conjunctiva – Redness	1.7	1.7	2	< 7 days	0
Conjunctiva – Chemosis	1	1	2	< 7 days	0
Conjunctiva – Discharge	0.3	1	1	< 72 hours	0
Corneal Opacity	1	1	1	< 7 days	0
Iridial Inflammation	0.7	0.7	1	< 72 hours	0

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

Remarks – Results	Slight iridial inflammation (grade 1) and slight corneal opacity (grade 1) was observed in both animals at the 24-hour observation and persisted to the 48-hour and 72-hour observation, respectively. Moderate conjunctival redness, swelling and discharge (grade 2) was observed at the 1-hour observation in both animals. Conjunctival redness (grade 2) persisted until the 48-hour observation and reduced to slight conjunctival redness (grade 1) at the 72-hour observation. Slight conjunctival swelling (grade 1) was observed at the 24-hour observation and persisted to the 72-hour observation. One animal displayed conjunctival discharge (grade 2), whereas the other rabbit had slight conjunctival discharge (grade 1) at the 24-hour observation. Slight conjunctival discharge (grade 1) was observed in one rabbit at the 48-hour observation. All effects resolved by the 7-day observation in both animals.
CONCLUSION	The assessed chemical is irritating to the eye.
TEST FACILITY	Envigo (2018g)

B.5. Skin Sensitisation – LLNA

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone: olive oil (4:1)
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde
Remarks – Method	No significant protocol deviations

RESULTS

Concentration (% v/v)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	5 F	982.8	1.0
25	5 F	1566.2	1.6
50	5 F	2738.4	2.8
100	5 F	3435.2	3.5
Positive Control			
25	5 F	7518.4	7.6

EC3 64.3%

Remarks – Results No unscheduled mortalities were observed. All animals showed expected body weight gains.

The stimulation index was > 3 in the 100% test group, indicating a sensitising response. The EC3 was calculated to be 64.3%.

Positive and negative controls performed as expected.

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

TEST FACILITY Envigo (2019b)

B.6. Repeat Dose Toxicity – Dose Range Finding Study

TEST SUBSTANCE Assessed chemical

METHOD In-house method

Species/Strain Rat/Wistar Han™:RccHan™:WIST

Route of Administration Oral – diet

Exposure Information Total exposure days: 14 days
Dose regimen: 7 days per week

Vehicle Diet

Remarks – Method For dose range finding purpose.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*			*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)**		
			Male	*Female*	
Control	5 per sex	0	0	0	0/10
Low Dose	5 per sex	5000	272	317	0/10
Mid Dose	5 per sex	10000	567	632	0/10
High Dose	5 per sex	20000	1067	1143	0/10

* Mean achieved dosage

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

No clinical signs of toxicity were noted.

There was a dose-related reduction in the total mean body weight and total mean food consumption that was observed in most animals of all dose groups between Days 1-4. Total mean body weight and total mean food consumption were comparable to the control or exceeded the control in all groups from Day 5 onwards with the exception of the mid-dose males, which also displayed a reduction in body weight gain from Days 11-15.

Effects in Organs

There was a statistically significant dose-dependent increase in absolute and relative liver weight for male animals of all treatment groups. In the males of the mid- and high- dose groups, a statistically significant dose-dependent increase in absolute and relative kidney weight was also observed.

A statistically significant increase in absolute and relative kidney weight was also observed in the female animals of the low-dose group. A decrease in the relative and absolute spleen weight was observed in all treatment groups for females and in the low-dose group for males. However, the study authors did not consider these effects as toxicologically significant due to the absence of a dose-related response.

An increase in pelvic space in the right kidney in one low dose male and an enlarged stomach with thickened tissue in the glandular and non-glandular regions in one mid-dose male were noted at necropsy. No other macroscopic pathologic abnormalities were noted at necropsy.

CONCLUSION

Based on the results in this study, 2500, 6000 and 12000 ppm were proposed for the subsequent combined repeated dose oral toxicity study with reproduction/developmental toxicity screening test.

TEST FACILITY Envigo (2018h)

B.7. Combined Repeated Dose Oral Toxicity Study with the Reproduction/Developmental Toxicity Screening Test – Rat

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (2016)

Species/Strain: Rat/Wistar (RccHan™;WIST)

Route of Administration: Oral – diet

Exposure Information: Total exposure days:

- Approx. 7 weeks for toxicity phase male animals (2 weeks prior to mating, during mating and until approx. 80% of the females had given birth)
- Approx. 5 weeks for toxicity phase female animals
- Approx. 8 weeks for reproductive phase females (2 weeks prior to mating, during mating and gestation and until day 13 of lactation).
- Approx. 5 or 7 weeks for high dose recovery female and male animals, respectively. Recovery phase females were not mated during the study; they were exposed to the test substance for an equivalent duration to the main group animals.

Dose regimen: 7 days per week

Post-exposure observation period: 14 days

Vehicle: None

Remarks – Method: No significant protocol deviations. Dose levels were selected based on the results of a dose-range finding study performed previously (see B.6 Repeat dose toxicity – Dose Range Finding Study).

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*			*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)**		
			Males	*Females*	
Control	15 F, 5 M	0	0	0	0/20
Low Dose	15 F, 10 M	2500	146	177 (183/376)	0/25
Mid Dose	15 F, 10 M	6000	342	420 (427/893)	0/25
High Dose	15 F, 5 M	12000	667	806 (838/1763)	0/20
Control Recovery	5/sex	0	0	0	0/10
High Dose Recovery	5/sex	12000	667	806	0/10

* Mean achieved dosage during toxicity/recovery phase (mean achieved dosage during gestation/lactation)

Mortality and Time to Death

There were no unscheduled deaths.

Effects on Parental Animals

There was no test substance-related effects on sensory reactivity, hindlimb grip strength, motor activity and water consumption.

Decreased mean forelimb strength was observed in both sexes of the high-dose animals in week 5 of treatment (82% for males and 91% for females) and week 2 of recovery (80% for males and 83% for females) in comparison to the control with statistical significant values achieved in male animals only. The decrease in mean forelimb strength observed in both weeks was attributed by the study authors to the reluctance of two male and two female rats in the high dose group to grip the forelimb bar; however, the relationship of this effect to treatment is unknown. No effect was observed in lactating reproductive phase females.

Dose-related reductions in body weight gain was observed in both sexes of all treatment groups on Days 1-2 of the study followed by weight gain in all groups on Day 3 observation. Compared to the control, statistically significant decreases in mean body weight in the mid- and high-dose males of the treatment and recovery groups were observed during Days 1-43 of treatment (76% and 61%, respectively). Decreases in mean body weight gains were also observed the low-dose males between Days 1-43 (87% compared to the control). Slight to moderately reduced mean body weight gain was observed in the females of the low and high dose treatment groups in comparison to the control (86% and 71%, respectively). During gestation, slightly reduced mean body weight was observed in the mid- and high-dose reproductive phase females (96% and 92%. respectively) followed by slightly increased mean body weight gain during lactation in all treatment groups compared to the control (1.19-, 1.16 and 1.22-fold increases, respectively). During recovery, high-dose males (2-fold increase) and females (1.3-fold increase) had higher mean weight gain in comparison to the control and by recovery Day 15, these values were slightly lower than the control (92% for males and 95% for females).

Food consumption initially decreased in a dose-dependent manner at the commencement of the study during Days 1-5 with a marked decreased in the high dose group animals. Decreased food consumption continued in all dose group males during treatment Day 1-43. From Treatment Day 5 to the end of the treatment period, food consumption remained similar to or slightly lower than the control in the females of all treatment groups during the toxicity and reproductive phases of the study, respectively. During recovery, the high dose males and females had similar food consumption to the control.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

The haematological examination of the peripheral blood revealed no toxicologically significant differences to the control.

Dose-related increases in blood levels of urea, cholesterol and total protein was observed in both sexes with statistical significance observed in mid- and/or high-dose toxicity phase males. Slight dose-related decreases in the blood levels of phosphorus was observed in toxicity phase females with statistical significance achieved in the high dose group only. Statistically significant increases in creatinine and triglyceride levels were also observed in high dose reproductive phase females on Day 13 of lactation. During the recovery phase, urea levels and cholesterol blood levels were comparable to the control in both sexes; however, total protein levels remained statistically higher than the control in females. Total protein levels and phosphorous levels were comparable to the control for recovery males and females, respectively.

Haematology revealed statistically significantly reduced prothrombin times were reported in all groups of treated males at the end of the administration period as well as statistically significant reductions in group mean white blood cell numbers were also observed in the mid- and high-dose females. However, the study authors deemed these effects as not treatment-related as there was no dose-response for the former and the latter was due to one atypically high value in the control group.

Urinalysis revealed a statistically significant dose-related increase in the total protein output, total glucose output and creatinine concentration in the mid- and high-dose males. Dose-related increases in total creatinine output was also observed in the mid- and high-dose males at treatment week 5. Statistical significant dose-related increases in protein concentration was also observed in high dose males. Increases in total glucose output in comparison to the control was observed in all female treatment groups at treatment week 5. At recovery week 2, all parameters were comparable to the control.

Effects in Organs
Macroscopic examination of the adult males and females showed no test-substance-related lesions.

All treated animals had increases in group mean body weight adjusted liver weights, with statistical significance observed for all males. Mean adjusted liver weights were comparable to the control for high-dose animals following 2 weeks recovery.

A dose-related increase in body weight adjusted kidney weights was observed in the toxicity phase males, with statistical significance observed for high-dose males. The adjusted kidney weights of all treated toxicity phase females were slightly higher than the control without apparent dose relationship. Following 2 weeks recovery, mean adjusted liver weights were comparable to the control in high-dose males while remained higher than the control in females.

Group mean body weight adjusted testes weights in all treated males were higher than the control and group mean adjusted combined seminal vesicle with coagulating gland weight in high-dose males were slightly lower than the control, without statistical significance or apparent dose relationship. The group mean adjusted testes and combined seminal vesicle and coagulating gland weights in high-dose recovery phase males were comparable to the control, following 2 weeks recovery.

The group mean body weight adjusted combined weight of the uterus, cervix and oviducts were low compared to the control in high-dose toxicity phase females. This effect was not considered to be test substance-related by the study authors as there was a strong correlation between the combined weight of the uterus, cervix and oviducts and stage of estrous at termination. A dosage-related decrease in the combined weight of the uterus, cervix and oviducts was observed in the reproductive phase females.

Microscopic examination of the kidneys revealed increases in the incidence of hyaline droplet accumulation in all treated toxicity phase males and nephropathy and an increase in tubular basophilia in the mid- and high dose toxicity phase males (compared to the control). In the recovery group, nephropathy, hyaline droplet accumulation and an increase in tubular basophilia was observed in the kidneys of some males. No test item-related findings were observed at microscopic examination for toxicity phase female animals.

Reproductive effects
There were no test substance-related effects for estrous cycle, male reproduction data (including male mating and fertility indices) and female reproduction and delivery data (including female mating and fertility indices, gestation index, live birth indices and post implantation loss).

Effects on pups
There were no test substance-related effects on litter data (including pup number and status at delivery, pup viability index/mortality and sex ratio), pup clinical observations, anogenital distance and anogenital distance index, nipple/areola and pup necropsy observations. However, there was a slight decrease in the overall mean body weight (between Days 1-13) of offspring derived from the mid and high-dose groups. No test substance-related effects were noted at macroscopic examination and histopathological investigations.

Remarks - Results
There were signs of systemic toxicity in the kidneys of the mid- and high-dose males (nephropathy), which were found to have associated effects such as:
- increases in body weight adjusted kidney weights
- dose-related increases in group mean urea concentration, total protein concentration, total protein output and total glucose output in the urine (of high-dose males)
- dose-related increases in protein concentration and glucose concentration in the urine
- dose-related decreases in the total creatinine output and a non-dosage related decrease in creatinine concentration in the urine.

The study authors stated that hyaline droplets are a common finding in the kidneys of untreated male rats. The increase in hyaline droplets observed in the kidneys of treated males was consistent with a test item associated increase in accumulation of alpha-2u-globulin. Hyaline droplet accumulation due to alpha-2u-globulin is both sex and species specific and is not generally considered to be significant in man.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established by the study authors as 2,500 ppm (equivalent to 146 mg/kg bw/day) for males and 12,000 ppm for females (equivalent to 806 mg/kg bw/day) based on the adverse effects in the kidneys of mid- and high dose treated males and the absence of test substance-related adverse effects up to the highest dose tested in females, respectively;

The NOAEL for reproductive/developmental toxicity was established by the study authors as 12,000 ppm (equivalent to 838 during mg/kg bw/day during gestation and 1763 mg/kg bw/day during lactation) based on there were no test substance-related reproductive/developmental effects up to the highest dose tested.

TEST FACILITY Covance (2019)

B.8. Genotoxicity – Bacteria

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997)
Plate incorporation (Test 1) and Pre incubation procedure (Test 2)

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

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

Concentration Range in Main Test
a) With metabolic activation:
Experiment 1: 1.5 – 5000 µg/plate
Experiment 2: 0.15 – 500 µg/plate
b) Without metabolic activation:
Experiment 1: 1.5 – 5000 µg/plate
Experiment 2: 0.05 – 150 µg/plate

Vehicle Acetone

Remarks – Method No significant protocol deviations. The dose range used for Experiment 2 was determined by the results of Experiment 1.

Negative control: Acetone
Positive controls:
With metabolic activation: 2-aminoanthracene (TA100, TA1535, TA1537, WP2uvrA); Benzo[a]pyrene (TA98)
Without metabolic activation: 4-nitroquinoline-N-oxide (TA98); N-methyl-N′-nitro-N-nitrosoguanidine (WP2uvrA, TA1535, TA100); 9-aminoacridine (TA1537)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	≥ 150	> 5000	negative
Test 2	-	≥ 150	> 150	negative
Present				
Test 1	-	≥ 150	> 5000	negative
Test 2	-	≥ 150	> 500	negative

Remarks – Results The test substance did not induce an increase in the frequency of revertant colonies in the test strains at any concentration, with or without metabolic activation.

The positive and negative controls gave a satisfactory response, confirming the validity of the test system.

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

TEST FACILITY Envigo (2018i)

B.9. Genotoxicity – *In Vitro* Chromosome Aberration Test

TEST SUBSTANCE Assessed 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 sulphoxide (DMSO)
Remarks – Method No significant protocol deviations. Dose selection for the main tests were based on the results of a preliminary test carried out at 6.1-1560 µg/mL.

Negative control: DMSO
Positive controls:
With metabolic activation: Cyclophosphamide
Without metabolic activation: Mitomycin C

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 25, 50, 100*, 150*, 200*, 250, 300	4 hours	20 hours
Test 2	0*, 6.25, 12.5, 25*, 50*, 75*, 100, 150	24 hours	24 hours
Present			
Test 1	0*, 25, 50, 100*, 150*, 200*, 250, 300	4 hours	20 hours

*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	≥ 390	> 200	> 300	negative
Test 2	≥ 97.5	> 75	> 150	negative
Present				
Test 1	≥ 390	> 200	> 300	negative

* Based on mitotic index ≥ 50%

Remarks – Results In main test 1, haemolysis was observed in the presence and absence of metabolic activation at dose concentrations ≥ 100 µg/mL and ≥ 50 µg/mL, respectively. In main test 2, haemolysis was observed at ≥ 50 µg/mL.

In the presence and absence of metabolic activation, there were no biologically relevant increases in structural chromosomal aberrations or polypoid cells after treatment with any dose of the test substance.

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

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

TEST FACILITY Envigo (2018j)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

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

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	2	7	81
14	5	14	91
25	35	25	-
28	63	28	-

Remarks - Results	All validity criteria of the test guideline were satisfied. The percentage degradation of the reference compound (sodium acetate) surpassed the threshold level of 60% after 14 days (70%). Therefore, the tests indicate the suitability of the inoculums. Oxygen depletion in the inoculum blank was 0.73 mg/L on day 28. The residual concentrations of oxygen in the test bottles were greater than 0.5 mg/L during the test period. The percentage biodegradation in toxicity control at day 14 was 65.7%. The degree of degradation of the test substance after 28 days was 63% and the 14 d window for Closed Bottle Test was met.
CONCLUSION	The assessed chemical is readily biodegradable.
TEST FACILITY	Nouryon (2019)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test Static
Species	Zebra fish *(Danio rerio)*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	145 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography (GC)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The test substance (1.02 g) was weighed and mixed with the test water (10 L) to produce stock test solution. This was further diluted to get nominal concentration of 5.0, 6.35, 8.06, 12.2, 13 and 16.5 mg/L.

RESULTS

Concentration mg/L *Nominal*	*Number of Fish*	*Mortality%* *24 h*	*48 h*	*72 h*	*96 h*
Control	7	0	0	0	0
5.0	7	0	0	0	0
6.35	7	0	0	0	0
8.06	7	0	0	0	0
10.2	7	43	43	43	43
13.0	7	100	100	100	100
16.5	7	100	100	100	100

LC50	10.4 mg/L at 96 hours (95% confidence limits 9.51 – 11.4 mg/L)
Remarks – Results	All validity criteria for the test were met. The dissolved oxygen concentration was within the range of 92 - 104% air saturation value throughout the test. The measured concentrations of the test solutions ranged from 93 to 105% which was maintained within 80%-120%. Therefore, the results are based on nominal concentrations. The 96 h LC50 for fish was determined by the Probit method.
CONCLUSION	The assessed chemical is harmful to fish.
TEST FACILITY	LEES (2019)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 202 *Daphnia sp*. Acute Immobilisation Test – Semi Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	245 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography Mass Spectrum (GC-MS)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. A nominal amount of test substance (100 mg) was dispersed in 1 litre of test water for 24 hours. Any undissolved test substance was removed by filtration to give a 100 mg/L stock solution. A geometric series (with a separation factor 2) of dilutions was made from this saturated solution to give the required test concentrations of 6.25, 12.5, 25, 50 and 100 mg/L. The test solution was renewed after 24 hours. Potassium dichromate was used as a reference substance.

RESULTS

Nominal concentration mg/L	*Number of D. magna*	*Immobilised* *24 h*	*48 h*
Control	20	0	0
6.25	20	0	0
12.5	20	1	1
25	20	11	18
50	20	20	20
100	20	20	20

EC50	18.6 mg/L at 48 hours (95% confidence limits 16.3 – 20.5 mg/L)

Remarks - Results	The EC50 value was calculated by Sigmoid dose response regression. All validity criteria for the test were satisfied. The dissolved oxygen concentration at the end of the test was equal to or greater than 3 mg/L in the control and test vessels. The 48 h EC50 = 2.03 mg/L for daphnids exposed to potassium dichromate was within the range of expected responses. The measured concentration was within 80-120% of the nominal concentration. The results are based on nominal concentration.
CONCLUSION	The assessed chemical is considered to be harmful to daphnia.
TEST FACILITY	NOACK (2018c)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 201 Freshwater Alga, Growth Inhibition Test - Static
Species	*Pseudokirchneriella subcapitata* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 0.36, 1.10, 3.3, 9.9, 29.7 and 89.1 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC-MS
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. A nominal amount of test substance (100 mg) was dispersed in 1 litre of test water for 24 hours. Any undissolved test substance was removed by filtration to give a 100 mg/L stock solution. A geometric series (with a separation factor 3) of dilutions was made from this saturated solution to give the required test concentrations of 0.367, 1.1, 3.3, 9.9, 29.7 and 89.1 mg/L. Potassium dichromate was used as a reference substance.

RESULTS

Biomass		*Growth*	
E_yC50	*NOEyC*	*E_rC50*	*NOE_rC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
9.06 (95% CL 3.63-21.7)	3.3	10 (95% CL 3.86-25.7)	3.3

Remarks - Results	All validity criteria for the test were satisfied. The cell concentration of the control cultures increased by 35-fold over the test period. The mean of the coefficients of variation of growth rates in the control cultures during the course of the test was ≤ 35%. The coefficient of variation of the average specific growth rate in replicate control cultures was 2.02%. The measured concentration was within 80-120% of the nominal concentration. The results are based on nominal concentration. All statistical analyses were performed using Sigmoidal dose response. The ErC50 = 1.09 mg/L was within the acceptable range for the reference substance.
CONCLUSION	The assessed chemical is considered to be toxic to algae.
TEST FACILITY	NOACK (2018d)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Aerated activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 10 - 1000 mg/L
Remarks – Method	Following a preliminary range-finding test, activated sewage sludge was exposed to an aqueous dispersion of the test substance at concentrations of 10, 32, 100, 320 and 1000 mg/L for a period of 3 hours at measured temperatures of approximately 20.2 °C. Copper (II) sulphate pentahydrate was used as the reference control.
RESULTS	
EC50	143 mg/L (95% CL 139 - 149 mg/L) at 3 hours
Remarks – Results	All validity criteria for the test were satisfied. The coefficient of variation of oxygen uptake in the control vessels was 3.62% and the specific respiration rate of the controls was 20.9 mg O_2/g.h. The reference substance gave a 3-hour EC50 value of 81.9 mg/L.
CONCLUSION	The assessed chemical is not inhibitory to microbial activity.
TEST FACILITY	NOACK (2018e)

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