File No.: LTD/2127

February 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4-Decenal, 5,9-dimethyl-

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2127	Firmenich Pty Ltd	4-Decenal, 5,9-dimethyl-	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information, the notified 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 notified chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Acute toxicity (Category 4)	H332 – Harmful if inhaled
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

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

Hazard classification	*Hazard statement*
Chronic (Category 1)	H400 – Very toxic to aquatic life with long lasting effects

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

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Acute toxicity (Category 4): H302 – Harmful if swallowed
  - Acute toxicity (Category 4): H332 – Harmful if inhaled
  - Skin irritation (Category 2): H315 – Causes skin irritation
  - Skin sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the engineering controls to minimise occupational exposure to the notified chemical during reformulation s:
  - Enclosed, automated systems, 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 notified 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 notified chemical during reformulation:
  - Protective clothing
  - Impervious gloves
  - Respiratory protection (if aerosols are formed)

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

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

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

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical collection and subsequent safe disposal.

Disposal

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

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the final use concentration of the notified chemical exceeds 0.7% in fine fragrances, 0.35% in deodorant, 5% concentration in air fresheners and 0.5% in other cosmetic products and household cleaning products;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

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

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details exempt from publication include: other names, analytical data, impurities and additives/adjuvants.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are varied for dissociation constant, flammability, explosive properties and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
Taiwan (2015), Philippines (2019), EU (2019), China (2019)

2. IDENTITY OF CHEMICAL

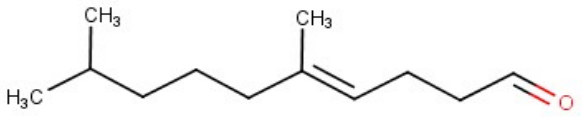
MARKETING NAME
4-Decenal, 5,9-dimethyl-

CAS NUMBER
689-65-6

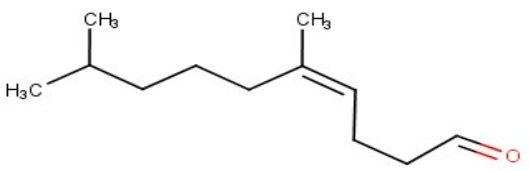
CHEMICAL NAME
4-Decenal, 5,9-dimethyl-

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

STRUCTURAL FORMULA
The notified chemical consists of two isomers:



4-Decenal, 5,9-dimethyl-, (E)- (CAS No. 18445-90-4) (**55.1%**)



4-Decenal, 5,9-dimethyl-, (Z)- (CAS No. 18445-82-4) (**43.8%**)

MOLECULAR WEIGHT
182.30 g/mol

ANALYTICAL DATA
Reference ^{1}H-NMR, ^{13}C-NMR, FTIR, GC-FID, GC-MS, 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*
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	236 °C at 98.2 kPa	Measured
Density	847 kg/m^3 at 20 °C	Measured
Vapour Pressure	4.98 × 10^{-3} kPa at 25 °C	Measured
Water Solubility	0.0148 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Hydrolytically stable in the environmental pH of 4-9	Measured
Surface Tension	71.5 mN/m	Measured
Partition Coefficient (n-octanol/water)	log Pow = 4.33 at 23.2 °C	
Adsorption/Desorption	log K_{oc} = 3.78 and 3.86 at 35 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	103 °C at 101.3 kPa	Measured
Flammability	Combustible liquid	Based on flashpoint
Autoignition Temperature	210 °C	Measured
Explosive Properties	Not explosive	Contain no functional groups that would infer explosive properties
Oxidising Properties	Not oxidising	Contain no functional groups that would infer oxidising properties

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

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

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

The notified chemical has a flash point of 103 ºC which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the notified chemical may be considered as a Class C2 combustible liquid if the chemical has a flash point below the boiling point.

5. INTRODUCTION AND USE INFORMATION

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

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

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

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER
Firmenich Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported neat, or as a component of fragrance formulations, in 5-180 kg closed lacquered drums. Within Australia the drums will be transported by road to the warehouse for storage and later distributed to the industrial customers by road for reformulation.

The notified chemical will also be imported as a component of finished consumer products at ≤ 5% concentration packed in containers suitable for retail sale. Finished consumer products containing the notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products at final use concentrations of ≤ 0.7% in fine fragrances, ≤ 0.35% in deodorant, ≤ 5% concentration in air fresheners and ≤ 0.5% in other cosmetic products and household cleaning products.

OPERATION DESCRIPTION
Reformulation of the notified chemical at ≤ 100% concentration may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end-use products into containers of various sizes.

End-use products containing the notified chemical at ≤ 5% concentration will be used by consumers and professionals such as hairdressers, beauticians 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
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	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, storage and warehouse workers may come into contact with the notified chemical in neat form or as a component of imported fragrance preparations or finished consumer products at ≤ 5% concentration, only in the unlikely event of accidental rupture of containers.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at up to 100% concentration may occur during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and use of personal protective equipment (PPE) by workers, such as protective clothing, goggles, impervious gloves and respiratory protection.

End-use
Exposure to the notified chemical in end-use products at ≤ 0.7% concentration may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hair dressers and workers in beauty salons), or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure 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 notified chemical.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 5% concentration through the use of a wide range of cosmetic, household products and air fresheners. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray ≤ 0.7% concentration.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the notified 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
Acute dermal toxicity – rat	LD50 = 2,000 mg/kg bw; low toxicity
Acute inhalation toxicity – rat	LC50 = 3.05 mg/L/4-hour; harmful
Skin irritation – *in vitro* reconstructed human epidermis model	non-irritating (no classification required)
Skin irritation – rabbit	irritating
Eye irritation – *in vitro* bovine corneal opacity and permeability assay	non-irritating (no classification required)
Eye irritation – rabbit	slightly irritating
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3 = 38%)
Repeat dose oral (gavage) toxicity – rat, 28 days	NOAEL = 1,000 mg/kg bw/day*
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test in human lymphocytes	non-clastogenic

*established by the study authors.

Toxicokinetics
Given its relatively low molecular weight (182.3 g/mol), the notified chemical may be absorbed across biological membranes.

Acute Toxicity
Based on acute toxicity studies conducted in rats, the notified chemical is harmful by the oral and inhalation routes but is of low acute toxicity by the dermal route.

In the acute oral toxicity study, 2/4 animals died or was killed *in extremis* during the study at a dose of 2,000 mg/kg bw of the notified chemical. The two animals that died or was killed *in extremis* showed at necropsy dark liver, dark kidneys, haemorrhage and epithelial sloughing in gastric mucosa of the stomach. Haemorrhage in the non-glandular epithelium in the stomach was also observed in the animal that died. No abnormalities were observed at necropsy for the surviving animals. At a dose of 300 mg/kg bw all five animals treated survived to the end of the study period.

In the acute inhalation toxicity study, 10/10, 5/10 and 0/10 animals died and/or were killed *in extremis* during the study when exposed nose-only to the notified chemical at concentrations of 5.0, 3.05 and 1.04 mg/L, respectively,

for 4 hours. In the animals that died or were killed *in extremis* during the study, the following macroscopic abnormalities were noted at necropsy: dark patches of the lungs, dark liver and gaseous distention in stomach, large intestine and small intestine. In surviving animals, dark patches of the lungs were noted in the two surviving females of the mid dose group and in all five males and two females of the low dose group. No macroscopic abnormalities were noted in the remaining three surviving females.

Although dark patches of the lungs were observed in most (100% high, 70% mid and 70% low dose animals) of the animals, there were no abnormalities detected during necropsy in the upper respiratory tract. The notified chemical is therefore not expected to be a respiratory irritant.

Irritation and Sensitisation
In an *in vitro* skin irritation study using the reconstructed human epidermis model (EpiSkin™), the notified chemical was determined not to warrant classification as a skin irritant under the GHS.

In a skin irritation study conducted in two rabbits, the notified chemical was found to be irritating. Well defined erythema (grade 2) was observed in both animals immediately after the exposure and persisted in both animals at the day 7 observation. The symptom extended to approximately 10 mm beyond the test site at the 1 hour to day 7 observations. In addition to this symptom, both animals showed light brown discolouration of the epidermis, loss of skin elasticity, and loss of skin flexibility at the day 7 observation. Glossy skin, desquamation and reduced growth of fur were observed in both animals at the day 14 observation. Slight (grade 2) oedema was observed in both animals immediately after the exposure and the symptom persisted at the day 7 observation. The symptoms warrant the notified chemical to be classified as a Category 2 skin irritant according to the GHS criteria.

The notified chemical is slightly irritating to eyes based on a study conducted in rabbits. Moderate conjunctival irritation was observed in all animals. All signs of irritation were resolved at the day 7 observation.

According to the results of an *in vitro* bovine corneal opacity and permeability (BCOP) assay, the notified chemical was determined not to warrant classification as an eye irritant under the GHS.

The notified chemical was found to be a weak skin sensitiser in a mouse local lymph node assay (LLNA), with an EC3 value of 38%.

Repeated Dose Toxicity
A repeated dose oral (gavage) toxicity study on the notified chemical was conducted in rats, in which the test substance was administered at 30, 300 and 1,000 mg/kg bw/day for 28 consecutive days, with a 14-day recovery period. The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 1,000 mg/kg bw/day. However, some statistically significant mean organ weights reported in low, mid, high and recovery groups were observed. Absolute and relative mean ovary weights of low, mid and high dose females were lower than the control group. Reduced mean absolute and relative spleen weights in low dose females were observed. The mean absolute weight of brain was lower in high dose recovery female than control recovery females, however, the mean relative weight of the brain in the same group was higher than control recovery female group. Moreover, the high dose recovery males showed increased absolute and relative heart weights than high dose recovery males

Mutagenicity/Genotoxicity
The notified chemical tested negative in a bacterial reverse mutation assay and in an *in vitro* chromosome aberration test in human lymphocytes.

Health Hazard Classification
Based on the available information, the notified 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 notified chemical is presented in the following table.

Hazard Classification	***Hazard Statement***
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Acute toxicity (Category 4)	H332 – Harmful if inhaled
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation
Exposure of workers to the notified chemical at ≤ 100% concentration may occur during blending operations, quality testing, and equipment cleaning and maintenance. The notified chemical is a weak skin sensitiser, irritating to the skin and slightly irritating to eyes. In addition, the notified chemical is acutely harmful via the oral and inhalation routes. Therefore, exposure control measurements should be used when handling the notified chemical at ≤ 100% concentration during reformulation.

Provided that control measures are in place to minimise worker exposure, including the use of enclosed, automated processes and personal protective equipment (PPE) such as impervious gloves, protective clothing and respiratory equipment (in cases where there is inadequate ventilation), the risk to the health of workers during the handling of the notified chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical at ≤ 0.7% 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 notified 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 notified chemical through the use of the cosmetic, household products and air fresheners containing the notified chemical at ≤ 5% concentration.

Acute toxicity and irritation
The notified chemical is harmful by the oral and inhalation routes, irritating to the skin and slightly irritating to eyes. However, these effects are not expected from the use of products containing the notified chemical at the proposed low use concentration in cosmetic and household products.

Sensitisation
Based on the results of an LLNA, the notified chemical is a skin sensitiser with an EC3 value of 38%. Using fine fragrances as a worst case example of leave-on cosmetic products that may contain the notified chemical (at ≤ 0.7% concentration), except for deodorants, the Consumer Exposure Level (CEL) is estimated to be 26.25 μg/cm^2/day (Cadby *et al*., 2002). For deodorants containing the notified chemical at ≤ 0.35% concentration, the CEL is estimated to be 26.25 μg/cm^2/day. Consideration of available information and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 26.82 μg/cm^2/day is estimated for the notified 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 deodorants at ≤ 0.35% concentration or fine fragrances at ≤ 0.7% concentration (a worst case example of other leave-on cosmetic products) is not considered to be unreasonable. Based on lower expected exposure level from other cosmetic products and household products, by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. However, it is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.7% in fine fragrances, ≤ 0.35% in deodorant, ≤ 5% concentration in air fresheners and ≤ 0.5% in other cosmetic products and household cleaning products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia; therefore there is no release of the notified chemical to the environment from this activity. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

In general, the reformulation processes are expected to involve automated blending operations in an enclosed environment, followed by packing of the finished products into end-use containers. During reformulation processes, limited release of the notified chemical is expected from cleaning of equipment as washings will be reused. A total of up to 0.2% of the import volume is estimated to be generated as waste from residues in empty containers and spills during reformulation. Empty containers containing the notified chemical will either be recycled or disposed of through an approved waste management facility.

Wastewater from reformulation equipment cleaning containing the notified chemical is expected to be disposed of to sewer via on-site wastewater treatment in accordance with local government regulations. Release of the notified chemical in the event of accidental spills or leaks during reformulation, storage and transport is expected to be collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic and household products. The notified chemical will be washed off the hair and skin of consumers as well as from cleaning activities and be released to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. The containers are expected to be disposed of through domestic garbage disposal and will enter landfill, or be subjected to recycling processes. Residues of the notified chemical in empty import and end-use containers are likely to either share the fate of the containers and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system and be treated at sewage treatment plants (STPs) before potential release to surface waters on a nationwide basis. A biodegradation study indicated that the notified chemical is considered to be rapidly biodegradable in the environment (76.9% degradation after 28 days), hence, it is expected to be degraded during the wastewater treatment process. For details of the biodegradation study, refer to Appendix C. Based on its adsorption coefficient values (log K_{oc} = 3.78 and 3.86 at 35 °C), partitioning to sludge is expected. The notified chemical has the potential to bioaccumulate based on its partition coefficient (log Pow = 4.33). However, due to its ready biodegradability, the notified chemical is not expected to bioaccumulate.

The notified chemical is expected to volatilise from water (log H = 1.78 Pa/m^3/mol) and is likely to partition to air during use or sewage treatment based on calculations for a representative component of the notified chemical. In the event of release to the atmosphere, the notified chemical is not expected to persist in the air compartment (half-life = 1.079 hours) based on calculations (AOPWIN v1.92; US EPA, 2012) for a representative component of the notified chemical.

A proportion of notified chemical may be applied to land when effluent containing the notified chemical is used for irrigation or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have moderate mobility based on its soil adsorption coefficient (log K_{oc} = 3.78 and 3.86 at 35 °C). In the aquatic and soil compartments, the notified chemical is expected to slowly 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 notified 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 notified chemical into sewer systems nationwide over 365 days per annum. The extent to which the notified chemical is removed from the effluent in STP processes based on the properties of the notified chemical has not been considered for this scenario, and therefore no removal of the notified 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%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.562 µg/L may potentially result in a soil concentration of approximately 3.7 µg/kg. Due to the notified chemical's ready biodegradability, annual accumulation is not expected.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 2.58 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 = 1.078 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 0.608 mg/L	Very toxic to algae
	72 h NOErC = 1.0 mg/L	Very toxic to algae with long lasting effects
Inhibition of Bacterial Respiration	3 h EC50 = 93.2 mg/L	Not inhibitory to bacterial respiration

Based on the ecotoxicological endpoints for the notified chemical, it is expected to be very acutely toxic to algae and acutely toxic to fish and aquatic invertebrates. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as "Acute Category 1; Very toxic to aquatic life". Since one chronic endpoint is available, the long-term hazard classification is determined by comparing the classification obtained from the acute endpoints and chronic endpoint and taking the most stringent outcome. In this case the most stringent outcome is based on the acute endpoints and the notified chemical is formally classified as "Chronic Category 1; Very toxic to aquatic life with long lasting effects".

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) has been calculated from the most sensitive endpoint for algae. A safety factor of 100 was used given acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
ErC50 (Algae, 72 h)	0.608	mg/L
Assessment Factor	100	
PNEC:	6.08	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	6.08	**0.09**
Q - Ocean	0.056	6.08	**< 0.01**

The conservative risk quotients (Q = PEC/PNEC) for the worst-case discharge scenario have been calculated to be less than 1 for both riverine and ocean compartments which indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity and use pattern. The notified chemical has a high partition coefficient (log Pow = 4.33), however, due to its ready biodegradability, it is not expected to bioaccumulate. On the basis of the PEC/PNEC ratio the notified chemical is not expected 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
Test Facility	Envigo (2016a)

Boiling Point 236 °C at 98.2 kPa

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

Density 847 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Determined using a pycnometer method.
Test Facility	Envigo (2016a)

Vapour Pressure 4.98×10^{-3} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure
Remarks	Determined using gas saturation method.
Test Facility	Envigo (2017a)

Water Solubility 0.0148 g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	NOACK (2016a)

Hydrolysis as a Function of pH

Method	OECD TG 111 Hydrolysis as a Function of pH EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH
Remarks	Under the conditions of the test, the test substance is expected to be hydrolytically stable in the environmental pH of 4-9.
Test Facility	Firmenich (2019)

Surface Tension 71.5 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions
Remarks	Concentration: 90% saturated solution
Test Facility	Envigo (2016a)

Partition Coefficient (n-octanol/water) log Pow = 4.33 at 23.2 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	The HPLC method was considered to be suitable for the purpose of the test since it showed two main peaks with well-defined and reproducible retention times. A weighted mean value was calculated on the basis of the respective peak area percentages.
Test Facility	NOACK (2016b)

Adsorption/Desorption log K_{oc} = 3.78 and 3.86 at 35 ± 1°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 test was performed at neutral pH.
Test Facility	Charles River (2019)

Flash Point 103 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Determined using closed cup method
Test Facility	Envigo (2017b)

Autoignition Temperature 210 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Test Facility	Envigo (2017b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure (2001)
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	No vehicle for 2,000 mg/kg bw treatment. Arachis oil BP for 300 mg/kg bw treatment.
Remarks – Method	No protocol deviations.

RESULTS

Sighting Study

Group	*Dose (mg/kg bw)*	*Evident Toxicity*	*Mortality*
1	2,000	No	0/1
2	2,000	Yes	2/4

Signs of Toxicity	No signs of toxicity were noted for the group 1 animal. One out of four females in group 2 was found dead one day after the administration of the test substance and another female from this group was killed *in extremis* 10 days after dosing. All group 2 animals showed hunched posture and tiptoe gait. Pilo-erection and/or decreased respiration rate was noted in three of these animals. The animal that was killed *in extremis* also showed laboured respiration, emaciation, lethargy, pallor of the extremities and hypothermia. The surviving animals appeared normal 2 days after dosing.
Effects in Organs	Dark liver, dark kidneys, haemorrhage and epithelial sloughing of the gastric mucosa were observed during necropsy in both animals that died on day 1 or was killed *in extremis* before the end of the study. In addition, haemorrhage of the non-glandular epithelium of the stomach was observed in the animal that died on day 1.
Remarks – Results	Normal bodyweight gain was observed in all the surviving animals except for a female in group 2 which showed no bodyweight gain during week 2.

Main Study

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

Discriminating Dose	300 mg/kg bw
Signs of Toxicity	No signs of toxicity were observed.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks – Results	The body weight gain of the treated animals was normal throughout the duration of the study. LD50 is > 300 mg/kg bw < 2,000 mg/kg bw.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	Envigo (2016b)

B.2. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test (1987)
Species/Strain	Rat/Wistar (RCCHan™;WIST)
Vehicle	Nil
Type of dressing	Semi-occlusive
Remarks – Method	No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	1M/1F	2,000	0/2
2	4M/4F	2,000	0/8

LD50	> 2,000 mg/kg bw
Signs of Toxicity – Local	Very slight to well-defined erythema, with or without very slight oedema, was noted in all animals one day after dosing. Very slight erythema, with or without very slight oedema, was noted in all animals 2 days after dosing. All signs of irritation were resolved 6 days after dosing. Light brown discolouration of the epidermis was also noted in three males up to 7 days after dosing.
Signs of Toxicity – Systemic	No systemic toxicity was observed.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks – Results	Normal bodyweight gain was observed in all animals except for a female in group 2 which showed a body weight loss during week 1 but expected gain in week 2.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	Envigo (2016c)

B.3. Acute Inhalation Toxicity – Rats

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009)
Species/Strain	Rats/RccHan™:WIST
Vehicle	Nil
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	liquid aerosol
Particle Size	Mass median aerodynamic diameter (MMAD): 2.17-2.25 µm
Remarks – Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (units)*		*Mortality*
		Nominal	*Actual*	
1	5M/5F	2.8	1.04	0/10
2	5M/5F	8.72	3.05	5/10
3	5M/5F	13.1	5.0	10/10

LC50	3.05 mg/L/4 hours (3.09 and 3.00 mg/L/4 hours for males and females, respectively).
Signs of Toxicity	All 10 high dose animals and five out of 10 mid dose animals (two males and 3 females) died or were killed *in extremis* during the study. Five out of 10 high dose animals (three males and two females) were found dead on days 7-9 post exposure. Two high dose males and three high dose

females were killed *in extremis* on days 8-10 post exposure. A mid dose male and a mid dose female were found dead on day 10 (male) and day 12 (female) post exposure. One male and two females from this group were also killed *in extremis* on day 12 post exposure.

Common clinical signs of toxicity observed in all exposure groups were wet fur, hunched posture, pilo-erection, lethargy and red/brown staining around the eyes during exposure and/or immediately after removal from the chamber. Most of the symptoms persisted in most high dose animals up to day 9 and/or 10 (all 10 high dose animals died or killed *in extremis* by day 10), in mid dose animals up to day 12 and in low dose animals up to 1 hour (hunched posture, however, persisted on day 1). A high dose female also showed exophthalmos (bulging of the eye) at 1 hour observation.

Reduced respiratory rate was observed in all animals in all treatment groups during exposure which intermittently persisted in mid dose animals up to days 4 and then 6 and/or 7 onwards and in high dose animals up to days 3 and then 7-9 (in one female the symptom persisted up to day 10). In three mid dose females the symptom persisted up to days 25 and/or 26. One female from this group also showed hunched posture and laboured respiration on day 28. Low dose animals showed the symptom only during exposure and 1 hour post exposure observations.

All high dose animals temperately appeared normal between days 4-6 and most of the above mentioned symptoms reappeared from day 7 post-exposure until death. No or only some symptoms were observed in all or most of the mid dose animals on days 5, 6, 9, 10 and 13-28. All low dose animals appeared normal from day 2 post-exposure.

Effects in Organs

Dark patches of the lungs were observed in all high dose animals, 7 (two that died – one male and one female; three killed *in extremis* – one male and two females; and two surviving females) mid dose animals and 7 (all five males and two females) low dose animals. The study authors stated no abnormalities were detected during necropsy in the upper respiratory tract.

Dark liver was observed in all high dose animals and 2 (one male and female that died) mid dose animals. Gaseous distention in stomach, large intestine and small intestine were observed in all high dose animals and 5 (two males and three females that died or were killed *in extremis*) mid dose animals.

No macroscopic abnormalities were noted in the remaining 3 surviving mid dose males and 3 low dose females.

Remarks – Results

Negative bodyweight gain was observed in all treated animals on day 1. Most of the high dose animals showed negative bodyweight gain until death. Bodyweight reductions were observed in two mid dose females and three low dose females on days 3-7 and days 7-14. No bodyweight gain in one mid dose female or minimal bodyweight gain in two low dose males was also observed. All other surviving animals showed expected bodyweight gain during the study.

Although dark patches of the lungs were observed in all treated animals, no abnormalities were detected during necropsy in the upper respiratory tract. The notified chemical is therefore not expected to be a respiratory irritant.

CONCLUSION

The notified chemical is harmful via inhalation.

TEST FACILITY Envigo (2016d)

B.4. Skin Irritation – *In Vitro* Reconstructed Human Epidermis Method

TEST SUBSTANCE Notified chemical

METHOD OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2015)
EPISKIN™ model
Vehicle Nil
Remarks – Method A pre-test using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide (MTT) showed the test substance does not directly reduce MTT.

Positive and negative controls were run in parallel with the test substance:
- Negative control: phosphate buffered saline with Ca^{2+} and Mg^{2+}.
- Positive control: sodium dodecyl sulphate (5% aqueous solution)

No significant protocol deviations.

RESULTS

Test Material	*Mean OD_{562} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	0.626	100	3.5
Test substance	0.722	115.3	18.4
Positive control	0.089	14.2	2.2

OD = optical density; SD = standard deviation

Remarks – Results Based on the mean tissue viability of > 50%, the notified chemical is not classified according to the test guidelines as a skin irritant, under the GHS.

Positive and negative controls performed as expected. The standard deviation of the relative mean variability values from the three test substance treated tissues was slightly greater (18.4%) than the upper limit of the assay acceptance criteria (≤ 18%). The acceptance criteria were not satisfied. However, as the relative mean viability results from the exposed tissues were negative for skin irritation effects, the study authors did not consider the slightly higher standard deviation to have affected the integrity or validity of the study.

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

TEST FACILITY Envigo (2017c)

B.5. Skin Irritation – Rabbit

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion (2015)
Species/Strain Rabbit/New Zealand White
Number of Animals 2 F
Vehicle Nil
Observation Period 14 days
Type of Dressing Semi-occlusive
Remarks – Method No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2	2	**	2	< 14 days	0
Oedema	2	2	**	2	< 14 days	0

* Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal
** tested only in two animals

Remarks – Results

Well defined erythema (grade 2) and slight oedema (grade 2) were observed in both animals immediately after exposure and up to and including the day 7 observation. The erythema extended to approximately 10 mm beyond the test site at the 1 hour to day 7 observations.

Both animals also showed light brown discolouration of the epidermis, loss of skin elasticity, and loss of skin flexibility at the day 7 observation.

Glossy skin, slight desquamation and reduced regrowth of fur were observed in both animals at the day 14 observation.

CONCLUSION

The notified chemical is irritating to the skin.

TEST FACILITY

Envigo (2016e)

B.6. Eye Irritation – *In Vitro* Bovine Corneal Opacity and Permeability Assay

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (2013)

Vehicle

Nil

Remarks – Method

Positive (ethanol) and negative (0.9% NaCl) controls were run in parallel with the test substance.

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues (SD)*	*Mean Permeabilities of Triplicate Tissues (SD)*	*IVIS (SD)*
Vehicle control	1.3	0.026	1.7
*Test substance**	1.7	0.025	2.0
*Positive control**	29.7	1.180	47.4

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

Remarks – Results

The IVIS of the test substance was 2.0. Based on an IVIS score of ≤ 3, the notified chemical is not classified according to the test guidelines as an eye irritant, under the GHS.

The controls gave satisfactory results confirming the validity of the test system.

CONCLUSION

The notified chemical was not considered irritating to the eye under the conditions of the test.

TEST FACILITY

Envigo (2016f)

B.7. Eye Irritation – Rabbit

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (2012)
Species/Strain	Rabbit/New Zealand White
Number of Animals	2M/1F
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	3			
Conjunctiva – Redness	1.7	2.0	1.7	2.0	< 7 days	0.0
Conjunctiva – Chemosis	1.3	1.3	1.3	2.0	< 7 days	0.0
Conjunctiva – Discharge	0.7	0.7	0.3	2.0	< 48 h	0.0
Corneal Opacity	0.0	0.0	0.0	0.0	-	0.0
Iridial Inflammation	0.0	0.3	0.0	1.0	< 48 h	0.0

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

Remarks – Results	Moderate conjunctival irritation was observed in all animals at the 1 and 24 hour observations with minimal conjunctival irritation observed at the 48 and 72-hour observations. Iridial inflammation was observed in two animals at the 1 and 24-hour observations, respectively. The symptom was resolved at the 48-hour observation. All signs of irritation were resolved at the day 7 observation. No corneal effects were observed.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Envigo (2016g)

B.8. Skin Sensitisation – LLNA

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010)
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil (4:1)
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde (25%) conducted in parallel with the test substance.
Remarks – Method	A preliminary test was conducted with one female using 100% test substance to justify the dose concentrations for the main study.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	5F	544.42	-
1	5F	903.91	1.66
10	5F	1454.69	2.67
25	5F	1218.08	2.24

100*	5F	2039.89	3.75
Positive Control			
25	5F	4619.6*	8.49

*Based on 4 animals due to exclusion of outlier by study author

EC3	38%
Remarks – Results	In the preliminary test, no signs of systemic toxicity or irritation based on a 25% increase in ear thickness were observed. Very slight erythema was noted on days 2 to 5. In the main test, very slight erythema was noted on days 2 and 3 with 100% test substance. No signs of systemic toxicity were noted in test and control animals. The stimulation index (SI) was > 3 at 100% concentration indicating a sensitising response. As no clear dose response was observed at 25% concentration, the EC3 value was calculated by the study authors based the 10% and 100% concentrations.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Envigo (2017d)

B.9. Repeat Dose Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)
Species/Strain	Rat/Sprague-Dawley Crl:CD® IGS BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Arachis Oil (BP)
Remarks – Method	In a previous range finding toxicity study, rats (number of animals exposed to the test substance not stated) were orally administered with the test substance at 250, 500 and 1,000 mg/kg bw/day for 7 days. No significant toxicological findings were observed.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5M/5F	0	0/10
Low Dose	5M/5F	30	0/10
Mid Dose	5M/5F	300	0/10
High Dose	5M/5F	1,000	0/10
Control Recovery	5M/5F	0	0/10
High Dose Recovery	5M/5F	1,000	0/10

Mortality and Time to Death

No unscheduled mortalities during the study period.

Clinical Observations

Increased salivation was observed in all 20 high dose animals from days 10-25. Chromodacryorrhea was observed in a low dose male on days 22-29 and in a high dose male on days 8-27. The study authors considered these findings in isolation as incidental.

Statistically significant reduction in overall motor activity was observed in low, mid and high dose males. High dose males also showed statistically significant reduction in the final 20% of the activity. In the absence of a

dose response and no such finding observed in females, this effect was not considered toxicologically significant by the study authors.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

The following statistically significant changes in mean values were observed:

Haematology:

- Increase in haemoglobin, red blood cell count, haematocrit in high dose males.
- Increase in mean corpuscular volume in mid dose males
- Reduction in mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration in high dose females
- Increase in neutrophils in high dose females

As no associated histopathological findings in bone marrow or spleen were observed and there were no similar findings in recovery animals at the end of the treatment free period, these findings were not considered to be toxicologically significant by the study authors.

In addition, a statistically significant increase in lymphocytes were observed in high dose recovery females at the end of the treatment free period. In the absence of a similar effect in animals of either sex at the end of the treatment period, this effect was not considered toxicologically significant by the study authors.

Blood chemistry:

- Reduction in glucose and chloride concentrations in high dose males. The study authors considered the effect on chloride concentration may be the result of increased water uptake. However, this effect was not observed in high dose females
- Increase in albumin and creatinine concentration in high dose males
- Reduction in triglycerides levels in high dose males
- Reduction in bilirubin contents in low, mid and high dose males and high dose females
- Increase in alanine aminotransferase level in low, mid and high dose females
- Increase in triglycerides levels in mid dose females
- Increase in urea and glucose content in high dose recovery females
- Slight reduction in albumin level in high dose recovery females

The study authors stated these findings have been observed following administration of enzyme inducing chemicals (Hall *et al* 2012). Although dose related effects were observed in certain parameters, these were considered to be associated with altered metabolism as a result of adaptive liver changes and were not considered toxicologically significant.

Effects in Organs

The following statistically significant effects were observed:

- Increase in absolute and relative mean liver weight in high dose males and females
- Reduction in absolute and relative mean ovary weights in low (27% and 12% reduction respectively compared to control group), mid (13% and 8% reduction respectively compared to control group) and high (15% and 12% reduction respectively than control group) dose females, mean absolute and relative spleen weights (23% and 16% reduction respectively than control group) in low dose females and
- Reduction (13% reduction compared to control group) in mean absolute and increase (38% increase compared to control group) in mean relative brain weights in high dose recovery females
- Increase in absolute and relative heart weights (11% and 15% increase respectively than control group) in high dose recovery males

The study authors stated as no associated histopathological changes were observed these findings were considered not toxicologically significant.

One high dose male showed enlarged kidneys at necropsy. However, no associated histopathological changes in kidneys were observed.

Enlarged liver with mottled appearance and midzonal vacuolation at microscopy were observed in a low dose male. The study authors stated that as findings were not observed in high dose males they were considered as

incidental and not treatment related. Enlarged liver was observed in a high dose male, however, no associated histopathological findings were observed. Minimal centrilobular hepatocyte hypertrophy was observed in three high dose males and three high dose females. This finding is commonly observed as an adaptive response to a xenobiotic.

Minimal follicular epithelial hypertrophy in thyroid was observed in four high dose females. The study authors stated that the changes observed were considered to be an adaptive physiological response of the thyroid gland to hepatic enzyme induction and due to the administration of high doses of xenobiotics (Capen et al 2002, Hall et al 2012 and Zabaka et al 2011).

The pathology study author concluded that the hypertrophic changes observed in liver and thyroid gland (in females) are considered to be linked. These findings are suggestive of an adaptive response to mixed function oxidase reduction in the liver (Cattley and Pope, 2002) and in the thyroid gland where the underlying mechanism is considered to be increased hepatic clearance of thyroid hormones (causing hypertrophy of follicular cells) (Capen *et al* 2002 and Zabka *et al.,* 2011). This correlates with the increase liver weights in high dose animals and the symptom reversed after the recovery period.

Slight cortical vacuolation of the adrenals was observed in one mid dose male, three high dose males and one high dose recovery male. The study authors stated this change is occasionally observed in males at low levels as a background change therefore the etiology is not clear. Zona glomerulosa hypertrophy of the adrenals was observed in one mid dose male, three high dose males, three high dose females and three high dose recovery females. The study authors stated the finding is generally considered to be adaptive and linked to fluid and/or electrolyte balance which may correlate with the increased water consumption observed in high dose animals. As this finding is occasionally, in general, observed in control animals, an association with treatment could not be prove and was therefore considered to be incidental by the study authors.

Remarks – Results

Statistically significant reduction in bodyweight gain was observed in high dose recovery females during first week of the treatment free period. However, no treatment related effects on food consumption was observed.

Mean water consumption was increased in high dose males and females (during weeks 3 and 4).

CONCLUSION

The NOAEL was established as 1,000 mg/kg bw/day by the study authors.

TEST FACILITY	Envigo (2017e)

B.10. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Pre incubation procedure
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	<u>Test 1</u> a) With metabolic activation:1.5, 5, 15, 50, 150, 500, 1,500 and 5,000 µg/plate b) Without metabolic activation: 0.05, 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1,500 and 5,000 µg/plate <u>Test 2</u> a) With metabolic activation: 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1,500 and 5,000 µg/plate b) Without metabolic activation: 0.015, 0.05, 0.15, 0.5, 1.5, 5, 15, 50 and 150 µg/plate
Vehicle	Dimethyl sulfoxide (DMSO)
Remarks – Method	Vehicle and positive control studies were conducted in parallel with the main study.

Vehicle controls: DMSO
Positive control: With metabolic activation: 2-aminoanthracene (TA100, TA1535, TA1537 and WP2uvrA), benzo(a)pyrene (TA98).

Without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguandine (TA100, TA1535 and WP2uvrA), 9-aminoacridine (TA1537), 4-nitroquinoline-1-oxide (TA98).

No significant protocol deviations.

RESULTS

Metabolic	*Test Substance Concentration (µg/plate) Resulting in:*			
Activation	*Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	Not investigated	≥ 15	> 5,000	Negative
Test 2	Not investigated	≥ 15	> 150	Negative
Present				
Test 1	Not investigated	≥ 150	> 5,000	Negative
Test 2	Not investigated	≥ 150	> 5,000	Negative

Remarks – Results

In test 2, without metabolic activation, statistically significant increase in the number of revertants in strain TA100 was observed at all concentrations tested. As no dose-response was observed, this increase was not considered to be biologically relevant by the study authors.

No biologically relevant increases in revertant colony numbers of any of the tester strains were observed during the test in either the presence or absence of metabolic activation.

The positive controls induced a distinct increase of revertant colonies during the study indicating the validity of the test system.

CONCLUSION

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

TEST FACILITY

Envigo (2017f)

B.11. Genotoxicity – *In Vitro* Chromosome Aberration Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (2014)

Species/Strain: Human
Cell Type/Cell Line: Lymphocytes
Metabolic Activation System: S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle: DMSO
Remarks – Method: Negative control: DMSO
Positive control: without metabolic activation: mitomycin
with metabolic activation: cyclophosphamide

In a preliminary dose range finding study, human peripheral lymphocytes were treated with the test substance at 7.12-1823 µg/mL for 4 hours and 24 hours without metabolic activation and for 4 hours with metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 0.88, 1.75, 3.5*, 7.0*, 10.5*, 14.0*, 17.5 and 21.0	4 h	24 h
Test 2	0*, 1.75, 3.5, 7.0*, 14.0*, 17.5*, 28.0*, 42.0 and 56.0	24 h	24 h
Present			
Test 1	0*, 1.75, 3.5, 7.0, 14.0*, 17.5*, 28.0*, 42.0* and 56.0	4 h	24 h

*Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 14.24	≥ 14	> 21	Negative
Test 2	≥ 28.48	≥ 17.5	> 56	Negative
Present				
Test 1	≥ 28.48	≥ 56	> 56	Negative

Remarks – Results

No statistically significant or biologically relevant increase in the number of cells with aberrations was observed at any concentrations, with or without metabolic activation. Further, no statistically significant or biologically relevant increase in the numbers of polyploidy cells was observed.

The positive controls behaved as expected, confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Envigo (2017g)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical oxygen demand (ThOD)
Remarks – Method	Conducted in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation**	*Day*	*% Degradation*
7	52.0	7	67.3
14	58.6	14	71.0
21	73.4	21	74.5
28	76.9	28	76.9

*Mean of two replicates

Remarks - Results	All validity criteria of the test guideline were satisfied. The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 14 days (71%). Therefore, the tests indicate the suitability of the inoculums. Oxygen uptake was 19.0 mg O_2/L in 28 days and did not exceed 60 mg/L. The pH was maintained between 7.52 – 7.74. The percentage biodegradation in the toxicity control at day 14 was 71.0%, hence it was concluded the test substance was not inhibitory to sludge microorganisms. The test substance degraded 76.9 % after 28 days and reached the pass level at the end of the 10 day window.
CONCLUSION	The test substance is readily biodegradable.
TEST FACILITY	SEC (2017)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test –Semi static
Species	Zebra fish (*Danio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	10 – 250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	Desired amounts of the test substance were weighed and mixed with the test water to produce test solutions with nominal concentrations of 0.8 mg/L, 1.1 mg/L, 1.5 mg/L, 2.2 mg/L, and 3.0 mg/L. The mixed solutions were stirred with a magnetic stirrer for about 2 hours and allowed to stand for 2 hours. The test solutions were prepared every 24 hours just before use.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Mortality*			
Nominal	*Measured*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7		0	0	0	0
0.8	0.342	7		0	0	0	0
1.1	0.926	7		0	0	0	0
1.5	1.447	7		0	0	0	0
2.2	2.155	7		0	0	0	0
3.0	3.094	7		5	7	7	7

*Geometric mean of fresh and old solutions

LC50 2.58 mg/L at 96 hours (based on geometric means of measured concentrations)

Remarks – Results All validity criteria for the study were met. The dissolved oxygen concentration was ≥ 80% of air saturation value throughout the test.

Since the deviation of the exposure concentrations of the test item was greater than 20% of the nominal concentrations, the results are based on the geometric means of the measured concentrations. Using the measured concentrations, the Trimmed Spearman-Karber method was used to calculate the 96 h LC50.

CONCLUSION The test substance is acutely toxic to fish.

TEST FACILITY SEC (2018)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test – Semi static

Species *Daphnia magna*

Exposure Period 48 hours

Auxiliary Solvent None

Water Hardness 250 mg $CaCO_3$/L

Analytical Monitoring HPLC

Remarks – Method An excess of the test substance (approx. 100 mg) was added directly to 1 L of test water. After 24 hours (± 1 hour) of gentle stirring in the dark at room temperature, the contents of the vessel was allowed to stand for 1 hour before use. The first 100 mL were discarded. Samples were taken from the remaining stock solution and chemically analysed. This stock solution was diluted to get the desired nominal concentrations.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Immobilised*	
Nominal	*Measured**		*24 h*	*48 h*
Control	Control	20	0	0
0.61	0.53	20	0	0
0.77	0.66	20	0	0
0.98	0.90	20	0	6
1.24	1.13	20	5	9
1.57	1.45	20	11	19
2.00	1.90	20	15	20

*Geometric means

EC50 1.078 mg/L at 48 hours (based on geometric means of measured concentrations)

Remarks – Results	All validity criteria were fulfilled. In the control, no daphnids became immobilised nor trapped at the surface of the water nor showed signs of stress. Dissolved oxygen concentration at the end of the test was ≥ 60% of the air-saturation value in controls and test vessels. Since the deviation of the exposure concentrations of the test substance was greater than 20% of the nominal concentrations, the results are based on the geometric means of the measured concentrations.
CONCLUSION	The test substance is acutely toxic to aquatic invertebrates
TEST FACILITY	LPL (2018a)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Freshwater Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata* (green algae)
Exposure Period	72 hours.
Concentration Range	Nominal: 0.25 – 5.1 mg/L Measured: 0.07 – 3.33 mg/L (geometric means)
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC-MS
Remarks - Method	No significant deviation in protocol were reported. Based on the results of a range-finding test, solutions were prepared by direct addition of the required amounts of stock solution to test water and inoculum to obtain the nominal concentrations space by a factor of approximately 2.

RESULTS

Biomass		*Growth*	
E_bC50 *mg/L at 72 h*	*NOE_bC* *mg/L*	*E_rC50* *mg/L at 72 h*	*NOE_rC* *mg/L*
0.204 (95 % CL 0.181 – 0.230)	0.110	0.608 (95% CL 0.522 – 0.721)	Not determined

Remarks – Results	All validity criteria for the study were satisfied. The cell density in the control increased 63 fold within 48 hours and increased 139 fold within 72 hours. The mean coefficient of variation for section-by-section specific growth rates in the control cultures was 26.0%. The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 5.1%. Since the deviation of the exposure concentrations of the test substance was greater than ± 20% of the nominal concentrations, the results were based on the geometric means of measured exposure concentrations after 48 and 72 hours.
CONCLUSION	The test substance is very toxic to algae
TEST FACILITY	LPL (2018b)

C.2.4. Inhibition of Microbial Activity

TEST SUBSTANCE	Notified 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 Actual: Not determined
Remarks – Method	Following a preliminary range-finding test, activated sewage sludge was exposed to an aqueous dispersion of the test substance at a concentration range of 10 – 1000 mg/L for a period of 3 hours. The measured temperature was approximately 21 °C with the addition of synthetic sewage as a respiratory substrate. Copper sulphate pentahydrate was used as the reference control. The respiration rate was determined by measurement of biological oxygen demand (BOD) during the test after 3 hours of exposure.
RESULTS	
EC50	93.2 mg/L at 3 hours (based on nominal concentrations)
Remarks – Results	All validity criteria for the test were satisfied. The coefficient of variation of oxygen uptake in the control vessels was 4.2% and the specific oxygen uptake rate of the controls was 20 mg O_2/g/hour. The reference substance gave a 3 hour EC50 value of 98 mg/L which was in the recommended range of 53 – 155 mg/L.
CONCLUSION	The test substance is not inhibitory to microbial activity
TEST FACILITY	NOACK (2016c)

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