File No: LTD/2062

March 2019

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4-Pentenoic acid, phenyl ester

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

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

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2062	Firmenich Pty Limited	4-Pentenoic acid, phenyl ester	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
Sensitisation, Skin (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 3)	H402 – Harmful to aquatic life

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 and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Acute toxicity (Category 4): H302 – Harmful if swallowed
  - Acute toxicity (Category 4): H332 – Harmful if inhaled
  - Sensitisation, skin (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 following engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - 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 processes:
  - 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 processes:
  - Protective clothing
  - Goggles
  - 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 adequate ventilation, physical collection and subsequent 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 concentration of the notified chemical exceeds or is intended to exceed 0.57% in fine fragrances, 0.25% in other cosmetic products, 5% in household cleaning products or 5% in air fresheners;

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 Limited (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, degree of purity, impurities, additives/adjuvants and use details.

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
None

2. IDENTITY OF CHEMICAL

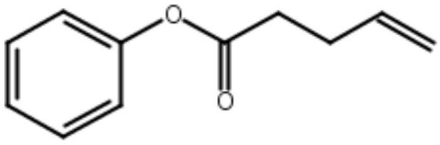
MARKETING NAME
Phenyl 4-pentenoate

CAS NUMBER
51231-09-5

CHEMICAL NAME
4-Pentenoic acid, phenyl ester

MOLECULAR FORMULA
$C_{11}H_{12}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
176.21 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 95 %

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: colourless liquid

Property	*Value*	*Data Source/Justification*
Freezing Point	< -20 °C	Measured
Boiling Point	244 °C at 98.2 kPa	Measured
Density	1,030 kg/m^3 at 20 °C	Measured
Vapour Pressure	3.17×10^{-3} kPa at 20 °C	Measured
Water Solubility	339 mg/L at 20 °C	Measured
Hydrolysis as a Function of pH	Less than 10% of test substance was hydrolysed at pH 2-7 (T=5 days). Complete hydrolysis occurs at pH 8.5.	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.76 at 20 °C	Measured
Surface Tension	63.5 mN/m at 20 °C	Measured. Not surface active
Adsorption/Desorption	log K_{oc} = 2.62 at 30 °C	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	114 °C at 101.5 kPa	Measured
Flammability	Not determined	Not expected to be highly flammable based on measured flash point
Autoignition Temperature	472 °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 oxidising properties

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

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

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

The notified chemical has a flash point of 114 ºC which is greater than 93 °C but less than its boiling point (244 ºC). Based on *Australian Standard AS1940* definitions for combustible liquid, the notified chemical may be considered as a Class C2 combustible liquid.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia neat 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 RECIPIENTS
Firmenich Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in neat form 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 a variety of cosmetic and household products at final use concentrations of ≤ 0.57% in fine fragrances, ≤ 0.25% in other cosmetic products and ≤ 5% in household cleaning products and air fresheners.

OPERATION DESCRIPTION
Reformulation of the notified chemical or fragrance formulations containing the notified chemical at ≤ 5% concentration into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes 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 preparations, 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 handling of drums, during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of personal protective equipment (PPE) such as protective clothing, goggles, respirator and impervious gloves.

End-use
Exposure to the notified chemical in end-use products at ≤ 5% 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 and household products. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables and these are based on information provided in various literatures (SCCS, 2010; Cadby et al., 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 100% was assumed for the notified chemical for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (Dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.25	1	0.3055
Face cream	1540	0.25	1	0.0602
Hand cream	2160	0.25	1	0.0844
Fine fragrances	750	0.57	1	0.0668
Deodorant spray	1430	0.25	1	0.0586
Shampoo	10460	0.25	0.01	0.0041
Conditioner	3920	0.25	0.01	0.0015
Shower gel	18670	0.25	0.01	0.0073
Hand soap	20000	0.25	0.01	0.0078
Hair styling products	4000	0.25	0.1	0.0156
Total				**0.6117**

C = maximum intended concentration of notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household products (Indirect dermal exposure - from wearing clothes):

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	5	0.25	10	0.1707
Fabric softener	90	5	0.25	10	0.0668
Total					**0.2375**

C = maximum intended concentration of notified 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	5	1980	0.01	0.01	0.007	0.0015
Dishwashing liquid	3	5	1980	0.0093	0.01	0.03	0.0125
All-purpose cleaner	1	5	1980	1	0.01	0.007	0.1083
Total							**0.1224**

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

Hairspray (Inhalation exposure):

Product type	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration zone 1 (min)	Exposure duration zone 2 (min)	Fraction inhaled (%)	Volume zone 1 (m^3)	Volume zone 2 (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	20	0.25	20	15	20	50	1	10	**0.0080**

C = maximum intended concentration of notified chemical

Total daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical at the maximum intended concentrations specified by the notifier in various product types. This would result in a combined internal dose of 0.9796 mg/kg bw/day for the notified chemical. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with low exposure factors (e.g. air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
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 = 3.18 mg/L/4 hour; harmful
Skin irritation – *in vitro* reconstructed human epidermis test	non-irritating
Eye irritation – rabbit	slightly irritating
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3 = 25.3%)
Repeat dose oral toxicity – rat, 28 days	NOAEL = 150 mg/kg bw/day*
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test in human lymphocytes	non genotoxic
Genotoxicity – *in vivo* micronucleus test	non genotoxic

* Functional observational battery changes were observed at all treatment groups compared to control on Day 28

Toxicokinetics

Given the low molecular weight (176.2 g/mol), moderate water solubility (339 mg/L at 20 °C) and partition coefficient (log Pow = 2.76 at 20 °C), the notified chemical may be absorbed across the dermal, respiratory or gastrointestinal tract.

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, 1/1 animals died at a dose of 2,000 mg/kg bw of the notified chemical whereas at a dose of 300 mg/kg bw all five animals tested survived to the end of the study period. The animal that died showed at necropsy dark liver, dark kidneys, gaseous stomach and epithelial sloughing of the gastric mucosa and non-glandular epithelium of the stomach. At 300 mg/kg bw, one animal showed epithelial sloughing of the gastric mucosa and non-glandular epithelium of the stomach. No abnormalities were observed at necropsy for the remaining animals.

In the acute inhalation toxicity study, 9/10, 3/10 and 0/10 animals died when exposed nose-only to the notified chemical at concentrations of 5.71, 2.6 and 0.95 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: abnormally dark patches or dark patches of the lungs, dark liver and gaseous distention in large and small intestine. In surviving animals, dark patches of the lungs were noted in the sole surviving animal of the high dose group and in two males and three females of the low dose group. No macroscopic abnormalities were noted in the

remaining surviving animals. Although dark patches of the lungs were observed there was no dose response and no abnormalities were detected during necropsy in the upper respiratory tract. The notified chemical is therefore not expected to be a respiratory irritant.

Irritation and Sensitisation
According to the results of an *in vitro* skin irritation assay, the notified chemical is not classified as a skin irritant. The notified chemical was found to be slightly irritating to the eyes of rabbits.

The notified chemical was found to be a weak skin sensitiser in a mouse local lymph node assay (LLNA), with an EC3 value of 25.3%.

Repeated Dose Toxicity
In a 28-day repeated dose oral toxicity study in rats, the notified chemical was administered through gavage at dose levels of 0, 30, 150 and 400 mg/kg bw/day. The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 150 mg/kg bw/day based on body tremors and reduction in body weight gains at 400 mg/kg bw/day. However, statistically significant reduction in grip in females and motor activity in males were reported in all treated groups compared to control groups.

Mutagenicity/Genotoxicity
The notified chemical showed negative results in a bacterial reverse mutation assay, an *in vitro* chromosome aberration test in human lymphocytes and in an *in vivo* micronucleus test.

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
Sensitisation, Skin (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 slight eye irritant and is considered to be a weak skin sensitiser. In addition, the notified chemical is acutely harmful via the oral and inhalation routes and systemic effects from repeated exposure are possible. Therefore, caution should be exercised when handling the notified chemical during the reformulation process.

Provided that control measures are in place to minimise worker exposure, including the use of automated processes and personal protective equipment (PPE) such as impervious gloves, protective clothing, safety glasses 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 ≤ 5% 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 and household products containing the notified chemical at ≤ 5% concentration.

Acute toxicity and irritation
The notified chemical is harmful by the oral and inhalation routes and it is a slight eye irritant. However, these effects are not expected from the use of products containing the notified chemical at the proposed use concentrations 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 25.3%. Using fine fragrances as a worst case example of leave-on cosmetic products that may contain the notified chemical (at ≤ 0.57% concentration), except for deodorants, the Consumer Exposure Level (CEL) is estimated to be 21.38 μg/cm^2/day (Cadby *et al*., 2002). For deodorants containing the notified chemical at ≤ 0.25% concentration, the CEL is estimated to be 18.75 μg/cm^2/day. Consideration of available information and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 21.72 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 ≤ 0.25% concentration or fine fragrances at ≤ 0.57% 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.

Repeated dose toxicity
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MOE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.9796 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 150 mg/kg bw/day derived from a 28-day repeated dose oral toxicity study on the notified chemical, the MOE was estimated to be 153. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.57% in fine fragrances, ≤ 0.25% in other cosmetic products, and ≤ 5% in household cleaning products and 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 notified chemical will be imported into Australia as a component of finished cosmetic and household products, or imported neat or as a component of fragrance formulations for reformulation into the end-use products. In general, the reformulation processes are expected to involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into end-use containers. Liquid waste from cleaning of the reformulation equipment will either be reused or disposed of through an approved waste management facility. Release of the notified chemical to the environment in the event of accidental spills or leaks during reformulation, storage and transport is expected to be absorbed on suitable materials and disposed of to landfill in accordance with local government regulations. Empty containers containing the notified chemical will be rinsed and then be recycled or disposed of through an approved waste management facility.

RELEASE OF CHEMICAL FROM USE
The notified chemical will be primarily washed into the sewers or released into the air during use of the various end-use products (e.g. shampoo, fabric softener, laundry detergent, air fresheners, cleaning formulations).

RELEASE OF CHEMICAL FROM DISPOSAL

Wastes and residues of the notified chemical in empty end-use containers are likely to either share the fate of the container and be disposed of to landfill, or be released to sewer when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic and household products, the majority of the notified chemical will enter the sewers and be treated at sewage treatment plants (STPs) before potential release to surface waters nationwide.

A ready biodegradation test determined that the notified chemical is readily biodegradable (72.65% after 28 days). For further details on the biodegradability study, refer to Appendix C.

The notified chemical is expected to be effectively removed at STPs due to its ready biodegradability. Approximately 31% of the notified chemical is expected to be released to surface waters. A proportion of the notified 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 notified chemical residues in landfill and soils are expected to have low mobility based on its calculated soil adsorption coefficient (log K_{oc} = 2.62). The notified chemical is not expected to be bioaccumulative based on its ready biodegradability and the calculated bioconcentration factor (BCF) of 30.8 L/Kg wet-wt. In the aquatic and soil compartments, the notified 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 Predicted Environmental Concentration (PEC) has been calculated based on a 100% release rate into the sewer system over 365 days per year. It is assumed that there is a 69% removal during the sewage treatment processes based on the physical and chemical properties. The resulting PEC in sewage is displayed in the table below.

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	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	69%	**Mitigation**
Daily effluent production:	4,877	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	0.17	µg/L
PEC - Ocean:	0.02	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 1.1 µg/kg.

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	LC50 2.12 mg/L	Harmful to fish
Daphnia Toxicity	EC50 3.05 mg/L	Harmful to daphnia
Algal Toxicity	EC50 16.6 mg/L	Harmful to algae
Inhibition of Bacterial Respiration (Nitrification Inhibition)	LC50 1.39 mg/L	Inhibits nitrification
Inhibition of Bacterial Respiration (Heterotrophic respiration)	LC50 306 mg/L	Not likely to be harmful to heterotrophic respiration

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be harmful to fish, algae 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 3; Harmful to aquatic life". Based on the acute toxicity, ready biodegradability and low bioaccumulation potential of the notified chemical, it is not formally classified under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the most sensitive end-point (Fish, LC50 2.12 mg/L) with an assessment factor of 10 as the endpoints for four trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish)	2.12	mg/L
Assessment Factor	10.00	
Mitigation Factor	1.00	
PNEC	212.00	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River	0.17	212	0.001
Q - Ocean	0.02	212	0.000

The risk quotient (Q=PEC/PNEC) has been calculated based on the assumption of complete release into the waterways. With a Q value much less than 1 for both river and ocean compartments the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on the proposed annual importation and use patterns. Therefore, on the basis of the predicted PEC/PNEC ratio, the maximum annual importation volume, and the assessed use pattern as a component of cosmetic and household products, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -20 °C

Method OECD TG 102 Melting Point/Melting Range
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Test Facility ERL (2016a)

Boiling Point 244 °C at 98.2 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 ERL (2016a)

Density 1,030 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 ERL (2016a)

Vapour Pressure 3.17×10^{-3} kPa at 25 °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 ERL (2017a)

Water Solubility 339 mg/L at 20 °C

Method OECD TG 105 Water Solubility
EC Council Regulation No 260/2014 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

pH	*T (°C)*	*Disappearance at 5 days*
2	40	< 10%
5	40	< 10%
7	40	< 10%
8.5	40	90%
12	40	100%

Remarks Less than 10% of test substance was hydrolysed at pH 2-7 (T=5 days). Complete hydrolysis occurs at pH 8.5.
Test Facility FSA (2012)

Partition Coefficient (n-octanol/water) log Pow = 2.76 at 20 °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 (2016b)

Surface Tension 63.5 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Concentration: 1,000 mg/L
Test Facility	ERL (2016a)

Adsorption/Desorption log K_{oc} = 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)
Test Facility	ERL (2016b)

Flash Point 114 °C at 101.5 kPa

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

Autoignition Temperature 472 °C

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

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

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

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method EC Directive92/69/EEC B.1bis Acute Toxicity (Oral) Fixed Dose Method
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	Arachis oil BP
Remarks – Method	No protocol deviations.

RESULTS

Sighting Study

Dose (mg/kg bw)	*Administered*	*Evident Toxicity*	*Mortality*
300	Gavage	No	0/1
2,000	Gavage	Yes	1/1

Signs of Toxicity	Hunchback posture was observed in the high dose animal at the 1 hour observation which persisted at the 4 hour observation. This animal was found dead one day after the administration of the test substance.
Effects in Organs	No signs of systemic toxicity were noted at a dose level of 300 mg/kg bw. The high dose animal showed dark liver, dark kidneys, gaseous stomach and epithelial sloughing of the gastric mucosa and non-glandular epithelium of the stomach. The animal treated with 300 mg/kg bw showed epithelial sloughing of the gastric mucosa and non-glandular epithelium of the stomach.

Main Study

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	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.

CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	ERL (2016c)

B.2. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	Nil
Type of dressing	Semi-occlusive
Remarks – Method	Dermal reaction observations were not performed on Day 4 on group 2 females. No significant 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	No dermal irritation was observed.
Signs of Toxicity – Systemic	No systemic toxicity was observed.
Effects in Organs	No abnormalities were observed during necropsy.
Remarks – Results	All animals showed expected body weight gains except for three females in Group 2 which showed a body weight loss or no gain during the first week but expected body weight gain during the second week.

CONCLUSION The notified chemical is of low acute toxicity via the dermal route.

TEST FACILITY ERL (2016d)

B.3. Acute Inhalation Toxicity – Rats

TEST SUBSTANCE Notified chemical

METHOD OECD TG 403 Acute Inhalation Toxicity

Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	Nil
Method of Exposure	Nose-only exposure
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	3.48, 2.46 and 2.59 µm for groups 1, 2 and 3, respectively.
Remarks – Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5M/5F	15.1	5.17	9/10
2	5M/5F	12.3	2.6	3/10
3	5M/5F	4.91	0.95	0/10

LC50	3.18 mg/L/4hours (3.67 and 2.72 mg/L for males and females, respectively)
Signs of Toxicity	In Group 1, 7/10 animals (4 males and 3 females) died or were killed *in extremis* during the exposure period with two further females killed *in extremis* prior to the one hour post exposure observation. In Group 2, 3/10 animals (one male and two females) died during the exposure period. No mortalities were observed in Group 3. Common clinical signs of toxicity observed in all exposure groups were decreased respiration rate, hunched posture, pilo-erection and wet fur. In addition there were frequent instances of increased respiration rate (Group 2 only) and red/brown staining around the snout, occasional instances of red/brown staining around the eyes and isolated occurrences of laboured respiration, ataxia, clonic convulsions, coma and lethargy were also noted. The surviving animals from Groups 1 and 2 appeared normal on Days 4 to 5 post-exposure. All Group 3 animals appeared normal on Day 2 post-exposure.
Effects in Organs	In surviving animals, dark patches of the lungs were noted in the sole

surviving animal of Group 1 and in two males and three females of Group 3. No macroscopic abnormalities were noted in the remaining animals of Group 3 and in all seven surviving animals from Group 2.

In the animals that died or were killed in extremis during the study the following macroscopic abnormalities were noted at necropsy: abnormally dark patches or dark patches of the lungs, dark liver and gaseous distention in large and small intestine.

Overall, dark patches of the lungs were observed in 9/10 animals of Group 1 (5 males and 4 females), 2 animals (2 females) of Group 2 and 5 animals (2 males and 3 females) of Group 3.

No abnormalities were detected during necropsy in the upper respiratory tract.

Remarks – Results

The one surviving animal from Group 1 showed no body weight gain on Day 1 following exposure. Normal body weight gains were observed during the remainder of the recovery period.

In Group 2, all surviving male animals and 1/3 surviving females exhibited body weight losses on Day 1 post-exposure. Normal body weight gains were observed during the remainder of the recovery period.

In Group 3, all males and one female animal exhibited body weight losses or showed no body weight gain on Day 1 post-exposure. Three female animals exhibited slight body weight losses from Days 3 to 7 post-exposure and one male exhibited a slight body weight loss during the final week of the recovery period.

Although dark patches of the lungs were observed there was no dose response and 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

ERL (2016e)

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

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method

Vehicle

Nil

Remarks – Method

Phosphate buffered solution and 5% sodium dodecyl sulphate were used as negative control and positive control, respectively.

The MTT tetrazolium salt [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was used to determine cell viability.

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	0.557	89.0	16.4
Positive control	0.089	14.2	2.2

OD = optical density; SD = standard deviation

Remarks – Results	The test substance was shown not to directly reduce MTT. The relative mean tissue viability for the test substance as compared to the negative control was 89%. As the relative mean tissue viability for the test substance was above 50%, it is considered a non-irritant. The positive and negative controls gave satisfactory results, confirming the validity of the test.
CONCLUSION	Based on the mean tissue viability of > 50%, the notified chemical is not classified as a skin irritant according to the GHS criteria.
TEST FACILITY	ERL (2016f)

B.5. Eye Irritation – Rabbit

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 F
Observation Period	72 hours
Remarks – Method	No signification 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	0.66	0.66	2	< 72 h	0
Conjunctiva – Chemosis	0.33	0.33	1	< 48 h	0
Conjunctiva – Discharge	0	0	1	< 24 h	0
Corneal Opacity	0	0	0	Nil	0
Iridial Inflammation	0	0	1	< 24 h	0

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

Remarks – Results	Slight (Grade 1) discharge and slight (Grade 1) iridial inflammation were observed in both treated eyes at the 1 hour observation. Moderate conjunctival irritation was observed in both treated eyes at the 1 hour observation with minimal conjunctival irritation at the 24 and 48-hour observations. Both treated eyes appeared normal at the 72-hour observation. Body weight loss was observed in one animal during the study.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	ERL (2016g)

B.6. Skin Sensitisation – LLNA

TEST SUBSTANCE	Notified 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 (not conducted in parallel)

Remarks – Method A preliminary study was conducted using 100% of the test substance. No signs of systemic toxicity, visual local skin irritation or irritation indicated by a greater than or equal to 25% increase in mean ear thickness were noted. Based on these results, the concentrations selected for the main study was 1%, 10% and 100%.

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	2178	-
1	5F	3872	1.78
10	5F	4567	2.10
100	5F	16078	7.38
Positive Control			
25	5F	21878	12.94

EC3 25.3%

Remarks – Results No unscheduled mortalities were observed. All animals made the expected body weight gain.

The stimulation index was > 3 in the 100% test group, indicating a sensitising response. The EC3 was calculated to be 25.3%.

Positive and negative controls performed as expected.

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

TEST FACILITY ERL (2017c)

B.7. Repeat Dose Oral Toxicity Study in Rats

TEST SUBSTANCE Notified chemical

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

Species/Strain Rat/Wistar (RccHanTM:WIST)

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 Concentration of the notified chemical for the main study was selected based on a previously conducted seven-day repeated oral gavage range finding study. The authors state severe clinical signs of toxicity (details not provided) were observed at 600 mg/kg bw/day and at 1,000 mg/kg bw/day. Reduction in body weight gain and food consumption were observed in males at 300 mg/kg bw/day and at 500 mg/kg bw/day. Females showed increased water consumption at 500 mg/kg bw/day. Based on these results the highest concentration selected for the main study was 400 mg/kg bw/day.

No protocol deviations.

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	150	0/10

High Dose	5M/5F	400	0/10
Control Recovery	5M/5F	0	0/10
High Dose Recovery	5M/5F	400	1/10

Mortality and Time to Death

A female from the high-dose recovery group was found dead on Day 2 prior to exposure. No clinical symptoms prior to death or no adverse findings at necroscopy were observed. The study authors states as body tremors were observed in 8/10 (4M/4F) of the high dose animals, the mortality could be considered as treatment related.

Clinical Observations

Body tremors were observed (4M/4F) in high-dose animals between Days 18-24.

The study authors stated that increased salivation and scabs observed in some control and treated animals were incidental and not treatment related.

Statistically significant reduction in fore limb grip in low dose (24.6% reduction than control group females) and hind limb grip in low (42% reduction than control group females), mid (30.6% reduction than control group females) and high (34.8% reduction than control group females) dosed females were observed in the first functional test out of three. The study authors stated that as these symptoms were observed in only one out of three tests and no dose related response was observed, these effects were not considered treatment related.

The overall motor activity in males in low (24% reduction than control group males), mid (14.6% reduction than control group males) and high (24% reduction than control group males) dosed groups were statistically significantly lower than the control group males when tested on Day 28. The study authors stated that as no dose response was observed and these effects were not observed in females, these symptoms were not considered treatment related.

In males at 400 mg/kg bw/day, a reduction in body weight gain (12%) was observed during Weeks 1, 3 and 4; however, statistical significance was not achieved. Five females out of 10 showed a reduction in body weight gain during the final week of treatment. During the recovery period, the body weight gain in both males and females of the high dose group was generally greater than controls, with statistical significance during the final week of the recovery period. There were no treatment related effects on food consumption.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

The following statistically significant findings were observed:

- increased platelet counts in low (18.4% increase than control group males), mid (32.6% increase than control group males) and high (24% increase than control group males) dose males and reduction in prothrombin time in females in all treatment groups (6%, 7% and 3.4% reduction in low, mid and high doses than control group females, respectively) groups.
- increased alanine aminotransferase (25.5% increase than control group males) and bile acids (159% increase than control group males) in high-dose males and increased (38% increase than control group females) bilirubin levels in high-dose females.
- increased calcium levels in mid (11.3% higher than control group males) and high-dose (10% higher than control group males) males.
- increased urea (32% higher than control group females), creatinine (11.4% higher than control group females) and potassium (17% higher than control group females) and reduction in albumin (7.5% lower than control group females) and calcium (4% lower than control group females) in high-dose females at the end of recovery period.
- increased (significantly higher than control males) gamma glutamyltranspeptidase in high-dose recovery males.

The study authors have not considered these changes to be of any toxicological significance.

Effects in Organs

A mass (~ 2mm x 3mm) was observed in left horn of the uterus in one of the mid-dose females. Microscopic examination showed presence of a cyst and moderate focal inflammation in thrombus. This finding was considered as incidental and not treatment related by the study authors.

The following statistically significant findings were observed:

- reduction in absolute and relative spleen weights in mid (26% and 33% less than control group males,

respectively) and high-dose (17.5% and 16% less than control group males, respectively) males.
- increase in absolute and relative heart and liver weights in high-dose (14% and 20% increase in heart weights and 21% and 25% increase in liver weights than control group males, absolute and relative weights, respectively) males at the end of recovery period.
- reduction in absolute kidney weights in low-dose females (30% less than control females).

The study authors stated that as there was no associated histopathological findings, the effects were incidental and not treatment related.

Three out of 5 males treated with high-dose showed cortical vacuolation in adrenals after the treatment period. Similar effects were also observed in two recovery control males and two recovery males treated with high-dose. The study authors stated these effects were not related to treatment.

CONCLUSION
The NOAEL established by the study authors is 150 mg/kg bw/day, based on body tremors and reduction in body weight gains at 400 mg/kg bw/day.

TEST FACILITY ERL (2017d)

B.8. Genotoxicity – Bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbital/β-napthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 0.5-5,000 µg/plate b) Without metabolic activation: 0.5-5,000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks – Method	Negative control: distilled water Positive control: with S9-mix: benzo(a)pyrene (TA98) and 2-aminoanthracene (TA100, TA1535, TA1537 and WP2uvrA) without S9-mix: *N*-methyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535 and WP2uvrA); 4-nitroquinoline-1-oxide (TA98); and 9-aminoacridine (TA1537). Preliminary toxicity test was not conducted.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 5,000	> 5,000	Negative
Test 2	-	> 5,000	> 5,000	Negative
Present				
Test 1	-	> 5,000	> 5,000	Negative
Test 2	-	> 5,000	> 5,000	Negative

Remarks – Results 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 significant 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 ERL (2017e)

B.9. Genotoxicity – *In Vitro* Chromosome Aberration Test in Human Lymphocytes

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain Human
Cell Type/Cell Line Lymphocytes
Metabolic Activation System S9 fraction from phenobarbital/β-napthoflavone induced rat liver.
Vehicle Dimethyl sulphoxide (DMSO)
Remarks – Method A preliminary experiment (at a concentration range of 6.88-1,763 µg/mL) was conducted to determine the dose range for the main test.

No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 27.5, 55*, 110*, 220*, 330* and 440	4	24
Test 2	0*, 27.5, 55*, 110*, 220*, 330* and 440	24	24
Present			
Test 1	0*, 27.5, 55, 110*, 220*, 330* and 440*	4	24

*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	≥ 440	> 440	> 440	Negative
Test 2	≥ 440	> 440	> 440	Negative
Present				
Test 1	≥ 881	> 440	440	Negative

Remarks – Results 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 and vehicle controls gave satisfactory responses confirming the validity of the test system.

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

TEST FACILITY ERL (2017f)

B.10. Genotoxicity – *In Vivo Micronucleus Test*

TEST SUBSTANCE Notified chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test
Species/Strain Rat/Wistar (RccHan™:WIST)
Route of Administration Oral – gavage
Vehicle Arachis oil BP
Remarks – Method The test was conducted at the end of the 28-day repeat dose toxicity study.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5M/5F	-	24
II (low dose)	5M/5F	30	24
III (mid dose)	5 M/5F	150	24
IV (high dose)	5M/5F	400	24
V (positive control, CP)	5 (sex not specified)	25	24

CP = cyclophosphamide.

RESULTS

Doses Producing Toxicity	Toxic effects (body tremors and reduction in body weight gains) were noted in the high dose group. For further details see B.7. There were no statistically significant decreases in the polychromatic to normochromatic erythrocyte ratio (PCE/NCE) in the test groups compared to the vehicle control group, indicating that bone marrow toxicity did not occur.
Genotoxic Effects	No increase in the incidence of micronucleated polychromatic erythrocytes was seen in the test groups.
Remarks – Results	In the repeat dose toxicity study, toxic effects were noted in the high dose group indicating that there was systemic exposure to the test substance. The positive control caused the expected increase in micronucleated cells, confirming the validity of the test system.

CONCLUSION The notified chemical was not clastogenic under the conditions of this *in vivo* micronucleus test.

TEST FACILITY ERL (2017g)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310: Ready Biodegradability - CO_2 in sealed vessels (Headspace Test)
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	none
Analytical Monitoring	Total Organic Carbon (TOC)
Remarks – Method	As per OECD test guidelines, no deviations were listed. Sodium benzoate was selected as reference substance.

RESULTS

Test Substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0.72		
4	43.40		
7	66.56		
11	73.62		
14	74.91	14	82.79
18	81.97		
21	75.66		
25	80.87	25	81.37
28	72.65		

Remarks – Results	Test substance reached > 60% theoretical inorganic carbon (ThIC) after 14 days and is therefore considered readily biodegradable. All validity criteria were met. Mean degradation of the reference substance was > 60% at day 14 and ThIC was < 3C/L in the blank controls.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Zhongke SX (2017a)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test -semistatic EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish - semistatic
Species	Brchydanio rerio (Zebra-fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	50 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV
Remarks – Method	As per OECD test guideline 203. No significant deviations were noted.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Mortality*					
Nominal	*Actual*		*3 h*	*6h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0	0
1.00	0.88	7	0	0	0	0	0	0
1.40	1.32	7	0	0	0	0	0	0
1.95	1.86	7	0	0	0	1	1	1
2.75	2.80	7	0	0	1	2	3	3
3.85	3.72	7	0	0	2	3	4	5
5.38	5.02	7	0	1	5	7	7	7

LC50	2.80 mg/L at 24 hours 2.20 mg/L at 48 hours 2.16 mg/L at 72 hours 2.12 mg/L at 96 hours
NOEC	1.32 mg/L at 96 hours
Remarks – Results	All validity criteria were met. O_2 concentrations were above 60% (78.6-103.1%). Concentration was maintained at > 80% of nominal concentration after renewal throughout the test and no mortality was detected in the control group.

CONCLUSION The notified chemical is considered to be harmful to fish.

TEST FACILITY Zhongke SX (2017b)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	none
Water Hardness	265 mg $CaCO_3$/L
Analytical Monitoring	HPLC-DAD
Remarks – Method	As per OECD test guideline 202, no significant deviations were recorded.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
Control	Control	20	0	0
10.0	4.62	20	8	17
5.00	1.80	20	7	15
2.50	1.02	20	0	7
1.25	0.494	20	0	5
0.625	0.400	20	0	1

LC50	> 10 mg/L at 24 hours 3.05 mg/L at 48 hours
NOEC	0.4 mg/L at 48 hours
Remarks – Results	Concentrations of the notified chemical were not maintained at 80% of the nominal value over the length of the study, therefore the geometric mean of the measured content was used to calculate ecotoxicity values. All validity criteria were met. pH did not deviate by more than 1.5 in each

replicate, dissolved oxygen was maintained at > 3 mg/L and temperature was maintained at 20 °C ± 1°C. No immobilisation was detected in the control group.

CONCLUSION The notified chemical is considered to be harmful to daphnia.

TEST FACILITY Noack (2017a)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
EC Council Regulation No 761/2009 C.3 Algal Inhibition Test

Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 7.90 – 40.0 mg/L Actual: 4.35 – 36.6 mg/L
Auxiliary Solvent	None
Water Hardness	Not determined
Analytical Monitoring	HPLC-DAD
Remarks – Method	According to OECD test guideline 201. Study was conducted three times; the first study was cancelled as analytical recoveries were below the level of quantification. The second study showed a decrease of test item over time in a non-concentration related manner. The third study also showed a decrease of test item over time in a non-concentration related manner, however the biological results for the inhibition of growth were not concentration related and not in accordance with previous testing. Therefore the results from study 2 were used.

RESULTS

Biomass		*Growth*	
EC50 (mg/L at 72 h)	*NOEC (mg/L)*	*EC50 (mg/L at 72 h)*	*NOEC (mg/L)*
8.14 (< 7.90-8.59)	< 7.90	16.6 (14.8-18.4)	< 7.90

Remarks – Results All validity criteria were met. Growth factor was 104 (1.55 specific growth rate), coefficient of variation was 17% for section-by-section growth and a coefficient of variation of 1.33% for specific growth rate.

CONCLUSION The notified chemical is considered to be harmful to algae.

TEST FACILITY Noack (2017b)

C.2.4. Inhibition of Microbial Activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 1.06 - 1000 mg/L Actual: 2.1 - 1000 mg/L
Remarks – Method	As per OECD guidelines, no variations were reported. A secondary study was conducted to determine the nitrification inhibition and heterotrophic respiration.

RESULTS

IC50 (Total respiration)	4.88 mg/L
NOEC (Total respiration)	< 1.06 mg/L
IC10 (heterotrophic respiration)	306 mg/L
NOEC (heterotrophic respiration)	32 mg/L
IC50 (Nitrification)	1.39 mg/L
NOEC (Nitrification)	< 1.06 mg/L
Remarks – Results	All validity criteria were met. Specific oxygen uptake rate was 23.1 mg O_2/g.h and the coefficient of variation between control replicates was 4%. The EC50 for the reference substance (copper (II) sulphate pentahydrate) was 97.6 mg/L.

CONCLUSION The notified chemical is inhibitory to nitrification

TEST FACILITY Noack (2017c)

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