File No: LTD/2067

March 2019

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Pyridine, 4-methyl-2-pentyl

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2067	Firmenich Pty Limited	Pyridine, 4-methyl-2-pentyl	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/polymer is presented in the following table.

Hazard Classification	*Hazard Statement*
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
Acute toxicity, inhalation (Category 4)	H332 – Harmful if inhaled
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

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 2)	H411 – Toxic to aquatic life with long lasting effects

Human Health Risk Assessment
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, oral (Category 4): H302 – Harmful if swallowed
  - Acute toxicity, inhalation (Category 4): H332 – Harmful if inhaled
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Serious eye damage/eye irritation (Category 1): H318 – Causes serious eye damage

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Adequate local exhaust ventilation

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

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

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

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

- If products and mixtures containing the 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 final use concentration of the notified chemical exceeds 0.05% in body lotion, face cream and hand cream, 0.1% in other leave-on/rinse-off cosmetics, 1% in fine fragrances, 0.1% in household cleaning products and 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(S)
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 not varied.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China (2018)

2. IDENTITY OF CHEMICAL

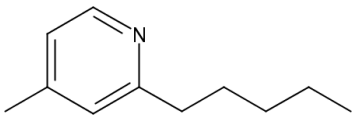
MARKETING NAME(S)
4-Methyl-2-pentylpyridine

CAS NUMBER
84625-54-7

CHEMICAL NAME
Pyridine, 4-methyl-2-pentyl-

MOLECULAR FORMULA
$C_{11}H_{17}N$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
163.26 g/mol

ANALYTICAL DATA
Reference NMR, IR, GC, 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	< -20 °C at 101.3 kPa	Measured
Boiling Point	214 °C at 101.3 kPa	Measured
Density	896 kg/m^3 at 20 °C	Measured
Vapour Pressure	6 × 10^{-3} kPa at 20 °C 1 × 10^{-2} kPa at 25 °C	Measured
Water Solubility	0.576 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not detected at pH 2, 5, 7, 8.5 and 12	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.76 at 20 °C	Measured
Surface tension	43.7 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 5.5 at 35 °C	Measured
Dissociation Constant	Not determined	The notified chemical contains pyridine functionality and is expected to become ionised in environmental conditions (pH 4-9).
Flash Point	98 °C at 101.3 kPa	Measured
Flammability	Combustible liquid[#]	Estimated
Autoignition Temperature	405 °C	Measured
Explosive Properties	Not explosive	Estimated
Oxidising Properties	Not oxidising	Estimated

Based on *Australian Standard AS1940 definitions*

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 physical 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 98 ºC which is greater than 93 °C but less than its boiling point of 214 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 be imported into Australia either in the neat form or as a component of fragrance formulations or finished consumer products.

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 RECIPIENT
Firmenich Pty Limited

TRANSPORTATION AND PACKAGING
The imported notified chemical or products containing it will be transported by road via truck to the notifier's warehouse or customers' facilities for storage or reformulation. Fragrance formulations containing the notified

chemical will be imported and distributed in lacquered drums of varying sizes from 5 – 180 kg. End-use products will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products at typical final use concentrations of ≤ 0.05% in body lotion, face cream and hand cream, ≤ 0.1% in other leave-on/rinse-off cosmetics, ≤ 1% in fine fragrances, ≤ 0.1% in household cleaning products and ≤ 5% in air fresheners.

OPERATION DESCRIPTION

Reformulation
The reformulation processes for incorporating the notified chemical into end-use products will likely vary depending on the specific type of cosmetic and household products formulated. This may involve both automated and manual processes including transferring and blending the notified chemical with other formulations. According to the notifier, a typical blending operation will be highly automated and occur in a fully enclosed/contained environment, followed by automated filling using sealed delivery systems into containers of various sizes.

End-use

Household products
Finished household cleaning products containing the notified chemical will be used by consumers and professional cleaners. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines or open processes, and manually applied by sponge, mop, spray or brush followed by wiping or rinsing.

Cosmetics
Finished cosmetic products containing the notified chemical will be used by consumers and professionals (such as hairdressers and workers in beauty salons). Depending on the nature of the product, application of products may be done by hand, sprayed or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	unknown	unknown
Mixing	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	0.5	1
Packaging	4	2
Professional end users	not specified	not specified

EXPOSURE DETAILS

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

Reformulation workers
During reformulation, dermal, ocular and possible inhalation exposure of workers to the notified chemical (at up to 100% concentration) may occur during weighing, transfer, blending, quality control analysis and cleaning/maintenance of equipment. Exposure is expected to be minimised through the use of local exhaust

ventilation and enclosed and automated systems, and through the use of personal protective equipment (PPE) such as impervious gloves, safety glasses, protective clothing and respiratory protection.

Professional end users
Exposure to the notified chemical in end-use products (at ≤ 5 % concentration) may occur in professions where the services provided involve the application of cosmetic products to clients or the use of cleaning products in the cleaning industry. The principal route of exposure is expected to be dermal, while ocular and inhalation exposures are also possible. Such professionals may use PPE to minimise repeated or prolonged exposure and ensure that good hygiene practices are 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 products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of a variety of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposures are also possible, particularly if products are applied by spray.

Data on typical use patterns of cosmetic and household products (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006) in which the notified chemical may be used are shown in the following tables. For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) of 100% was assumed for the notified chemical for calculation purposes (ECHA, 2014). For the inhalation exposure assessment, a 2-zone approach was applied (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%. For calculation purposes, a lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used.

Cosmetic products (Dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.05	1	0.0611
Face cream	1,540	0.05	1	0.0120
Hand cream	2,160	0.05	1	0.0169
Fragrances	750	1	1	0.1172
Deodorant (non-spray)	1,500	0.1	1	0.0234
Shampoo	10,460	0.1	0.01	0.0016
Hair conditioner	3,920	0.1	0.01	0.0006
Shower gel	18,670	0.1	0.01	0.0029
Hand wash soap	20,000	0.1	0.01	0.0031
Hair styling products	4,000	0.1	0.1	0.0063
Total				**0.2452**

C = concentration (%); RF = Retention Factor
Daily Systemic Exposure = (Amount × C × RF × dermal absorption)/body weight

Hair spray (inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.1	20	1	20	50	1	10	**0.0032**

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 1 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

Household products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.1	0.95	10	0.0034
Fabric softener	90	0.1	0.95	10	0.0013

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Total					**0.0048**

Daily Systemic Exposure = (Amount × C × PR × PT)/body weight

Household products (Direct dermal exposure – from wearing clothes)

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.1	1,980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.1	1,980	0.009	0.01	0.03	0.0003
All-purpose cleaner	1	0.1	1,980	1	0.01	0.007	0.0022
Total							**0.0024**

Daily Systemic Exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale factor × dermal absorption)/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. This would result in a combined internal dose of 0.2556 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposures.

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 (class method)	LD50 = 300 – 2000 mg/kg bw; harmful
Acute dermal toxicity – rat (limit test)	LD50 > 2000 mg/kg bw; low toxicity
Acute inhalation toxicity – rat	LC50 = 3.83/4.04 (M/F) mg/L/4-hour; harmful
Skin irritation – *in vitro* reconstructed human epidermis model	irritating
Skin corrosion – *in vitro* reconstructed human epidermis model	non-corrosive
Eye irritation – *in vitro* bovine opacity and permeability assay	irritating
Skin sensitisation – guinea pig, maximisation test according to Magnusson and Kligman	no evidence of sensitisation
Combined repeat dose oral toxicity and reproductive and developmental toxicity – rat	repeated dose NOAEL = 105 mg/kg bw/day reproductive and developmental NOAEL = 35 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test	non genotoxic

Toxicokinetics

No data on toxicokinetics for the notified chemical was provided. For dermal absorption, molecular weights below 100 g/mol are favourable for absorption and molecular weights above 500 g/mol do not favour absorption (ECHA, 2017). Dermal uptake is likely to be moderate to high if the water solubility is between 100-10,000 mg/L and the partition coefficient (log P) values between 1 and 4 (ECHA, 2017). Based on the low molecular weight (163.26 g/mol), water solubility (0.576 g/L) and partition coefficient (log Pow = 3.76 at 23.1 °C) of the notified chemical, absorption across biological membranes may occur.

Acute Toxicity

The notified chemical was found to be harmful via the oral route when tested in rats. Two animals treated at 2000 mg/kg died (1 animal was found dead and the other was humanely killed due to poor clinical condition). There were no mortalities or clinical signs for animals treated at 300 mg/kg.

The notified chemical was of low acute dermal toxicity when tested in rats.

The notified chemical was found to be harmful via the inhalation route. The LC50 was 4.04 mg/L/4-hour for males and 3.83 mg/L/4-hour for females. There were no abnormal macroscopic findings in the upper respiratory tract reported following necropsy.

Irritation
According to the results of two *in vitro* assays using reconstructed human epidermis models, the notified chemical is considered non-corrosive but irritating to skin, requiring hazard classification (GHS Category 2).

According to the result of an *in vitro* bovine corneal opacity and permeability assay, the notified chemical is considered to cause serious damage to eyes, requiring hazard classification (GHS Category 1).

Sensitisation
The notified chemical was not a skin sensitiser in guinea pigs when tested in a maximisation test (induction and challenge by topical administration at 50% and 20% concentrations, respectively).

Repeated Dose Toxicity
In a combined repeated dose oral (gavage) toxicity study with the reproduction/developmental toxicity screening test the notified chemical was administered to rats at 12, 35 and 105 mg/kg bw/day for at least 6 weeks with a 2 week recovery.

The systemic No Observed Adverse Effect Level (NOAEL) was established as 105 mg/kg bw/day (the highest dose tested) in this study, based on no treatment-related adverse findings were noted at all doses tested.

The reproductive/developmental NOAEL was established as 35 mg/kg bw/day, based on statistically significant lower mean post implantation survival index, lower mean live litter sizes, and slower growth of the female offspring noted at the higher dose level (105 mg/kg bw/day).

Mutagenicity/Genotoxicity
The notified chemical showed negative results in a bacterial reverse mutation assay and an *in vitro* chromosomal aberration test using 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, oral (Category 4)	H302 – Harmful if swallowed
Acute toxicity, inhalation (Category 4)	H332 – Harmful if inhaled
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation
During reformulation, worker exposure will be limited through the use of engineering controls (such as enclosed, automated systems and local exhaust ventilation) and appropriate PPE (eye protection and respiratory protection if inhalation exposure may occur), as stated by the notifier.

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.

End-Use
Workers involved in professions where the services provided involve the application of cosmetic and household products containing the notified chemical to clients (*e.g.* hairdressers, beauty salon workers and cleaners) or the use of household products in the cleaning industry may be exposed to the notified chemical at ≤ 0.05% concentration. PPE may be employed by workers to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that for consumers using various products containing the notified chemical.

6.3.2. Public Health
Members of the public will experience widespread and frequent exposure to the notified chemical at ≤ 1% concentration through daily use of cosmetic and household products and up to 5% from air fresheners. The main route of exposure is expected to be dermal and inhalation, with some potential for accidental ocular or oral exposure.

Eye and skin irritation
The notified chemical is a severe eye irritant and skin irritant. However, risk of eye and skin irritation effects are not expected at the proposed low concentrations in end-use products (< 1%). Scheduling of the chemical may be required if consumer products will contain the chemical at a concentration of 1% or above (GHS cut-off for chemicals classified as Cat 1 for eye effects) unless toxicity data for the product shows no severe eye damage at the higher concentrations.

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 as 0.2556 mg/kg bw/day (see Section 6.1.2). Using the lowest NOAEL of 35 mg/kg bw/day derived from a 28-day repeated dose oral toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 136.9. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Based on the potential systemic exposure from the notified chemical in cosmetic and household products, an MOE value greater than or equal to 100 is also expected where the notified chemical is present at concentrations of ≤ 0.05% in body lotion, face cream and hand cream, ≤ 0.1% in other leave-on/rinse-off cosmetics, ≤ 1% in fine fragrances, ≤ 0.1% in household cleaning products and ≤ 5% in air fresheners..

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

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical is not manufactured in Australia, therefore there is no environmental release associated with this activity. Environmental release is only likely during transportation, storage, reformulation and repackaging of the notified chemical and is estimated by the notifier as 0.1% of the import volume Environmental release from reformulation is expected to be minimal as the reformulation process is highly automated in a controlled environment. The notified chemical in waste water from washing equipment and residues in empty containers are recycled to the extent practicable or disposed of through a licensed contractor.

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 and cleaning formulations).

RELEASE OF CHEMICAL FROM DISPOSAL
Waste from spills during transportation and reformulation are to be disposed of to landfill. Some of the notified chemical is also expected to be disposed of to landfill and recycling through the disposal of the empty containers.

7.1.2. Environmental Fate

The notified chemical will enter sewers and be subsequently treated at sewage treatment plants (STPs) following its use in products available to the general public (e.g. shampoo, fabric softener, detergents and air fresheners).

A ready biodegradation test determined that the notified chemical is not biodegradable (0% after 28 days).

The notified chemical is expected to be partially removed at STPs. Approximately 77% of the notified chemical is expected to be released to surface waters. The notified chemical is not expected to bioaccumulate based on the calculated bioconcentration factor (BCF) of 38-48 L/Kg. See Appendix C for study details.

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. A worst case scenario is assumed where there is no removal during the sewage treatment processes. 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	1,000.000	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

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	EC50 12.7 mg/L	harmful to fish
Daphnia Toxicity	EC50 5.71 mg/L	toxic to invertebrates
Algal Toxicity	EC50 6.4 mg/L	toxic to algae
Inhibition of Bacterial Respiration	EC50 89 mg/L	harmful to bacterial respiration

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be acutely toxic to aquatic life. However, as the notified chemical is not biodegradable the effects are expected to be long lasting. Therefore, the notified chemical is formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) as chronic Category 2.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the most sensitive end-point (Algae, LC50 5.71 mg/L) with an assessment factor of 100 as the endpoints for four trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Invertebrates).	5.71	mg/L
Assessment Factor	100.00	
Mitigation Factor	1.00	
PNEC:	57.10	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	0.56	57.1	0.01
Q - Ocean:	0.06	57.1	0.001

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 it is highly unlikely that the notified chemical will reach ecotoxicologically significant concentrations based on the proposed annual importation and use patterns.

On the basis of the PEC/PNEC ratio, reported use pattern and low import volume, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -20 °C at 101.3 kPa

Method OECD TG 102 Melting Point/Melting Range
Remarks Determined to be < -20 °C due to test substance froze when stored at -80 °C
Test Facility WIL (2015a)

Boiling Point 214 °C at 101.3 kPa

Method OECD TG 103 Boiling Point
Remarks Determined by differential scanning calorimetry
Test Facility WIL (2015a)

Density 896 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids
Remarks Pycnometer method
Test Facility WIL (2015a)

Vapour Pressure 6×10^{-3} kPa at 20 °C
1×10^{-2} kPa at 25 °C

Method OECD TG 104 Vapour Pressure
Remarks Isothermal thermogravimetric effusion method
Test Facility WIL (2015b)

Water Solubility 576 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 DR.U. Noack-Laboratorien (2015a)

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)*	*$t_{½}$ <hours or days>*
2	40	N/A
5	40	N/A
7	40	N/A
8.5	40	N/A
12	40	N/A

Remarks Less than 10% hydrolysis detected after 5 days and 28 days at all pH levels.
Test Facility Firmenich S.A Geneva (no date)

Partition Coefficient (n-octanol/water) log Pow = 3.76 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 DR.U. Noack-Laboratorien (2015b)

Surface Tension 43.7 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions
Remarks	Concentration: 90% of the saturation level
Test Facility	WIL (2015c)

Adsorption/Desorption log K_{oc} = 5.5 at 35 °C at neutral pH

Method	OECD Guideline for the Testing of Chemicals no. 121: "Estimation of the Adsorption Coefficient (K_{oc}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)". The test was conducted at neutral and pH 8.
Remarks	UPLC was used instead of HPLC.
Test Facility	WIL (2015d)

Flash Point 98 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Closed cup method
Test Facility	WIL (2015a)

Autoignition Temperature 405 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Test Facility	WIL (2015e)

Explosive Properties Not explosive

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	The molecular structure was assessed to contain no chemical groups which are associated with explosive properties.
Test Facility	WIL (2015e)

Oxidizing Properties Not oxidising

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks	The molecular structure was assessed to contain no chemical groups that could act as an oxidising agent.
Test Facility	WIL (2015e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Wistar RccHan:WIST
Vehicle	Corn oil
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3F	300	0/3
2	3F	2000	2/3

LD50	300 - 2000 mg/kg bw
Signs of Toxicity	Two animals treated at 2000 mg/kg bw died on Day 3. Clinical signs prior to death were seen from Day 2 and included piloerection, decreased activity, cold to touch, shallow breathing, partially closed eyelids (both eyes), reduced body tone and flattened posture. Clinical signs seen in the surviving female treated at 2000 mg/kg were noted from Day 1 and included salivation, piloerection and hunched posture. This animal had recovered by Day 7. There were no mortalities or clinical signs for animals treated at 300 mg/kg bw.
Effects in Organs	Macroscopic examination of the animals that were treated at 2000 mg/kg and died prior to the scheduled necropsy revealed atrophy of the cecum, spleen and liver, pallor of the kidneys, liver, lungs and spleen, yellow fluid content in the large and small intestines, an enlarged stomach (containing food) and congestion (characterised by darkened tissues) of the subcutaneous tissue. No abnormalities were noted in any surviving animal at the macroscopic examination at study termination on Day 15.
Remarks – Results	A loss in body weight was noted for the 2 animals that were treated at 2000 mg/kg bw and died. A loss in bodyweight was noted in the surviving animal treated at 2000 mg/kg bw on Day 8; however, a satisfactory bodyweight gain was noted between Days 8-15. All animals treated at 300 mg/kg achieved satisfactory body weight gains throughout the study.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	HLS (2015)

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	None
Type of dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations. A preliminary study (Group 1) was conducted in 1 male and 1 female animal at a dose of 2,000 mg/kg bw. The dose of 2,000 mg/kg bw was selected for the Group 2 study based on the results of the Group 1 study (no mortality or significant toxicity).

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	1 per sex	2000	0/2

2	4 per sex	2000	0/8

LD50	> 2000 mg/kg bw
Signs of Toxicity – Local	No signs of dermal irritation were noted in animals of Group 1. Very slight erythema and edema were noted at the test sites of all animals of Group 2 up to 5 days after dosing. Crust formation was also noted at the test sites of 3 females 3-8 days after dosing.
Signs of Toxicity – Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted in the animals of Group 1 at necropsy. Patchy pallor of the liver was noted in all animals of Group 2 at necropsy.
Remarks – Results	All animals showed expected gains in body weight.

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

TEST FACILITY Envigo (2015a)

B.3. Acute Inhalation Toxicity – Rat

TEST SUBSTANCE Notified chemical

METHOD OECD TG 403 Acute Inhalation Toxicity

Species/Strain	Rat/RccHan:WST
Vehicle	None
Method of Exposure	Nose-only exposure
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	Mean MMAD: 3.09 µm (Group 1), 2.99 µm (Group 2), 3.19 µm (Group 3), 2.69 µm (Group 4)
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration (units)*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	7.71	3.02	3/10
2	5 per sex	14.8	3.49	4/10
3	5 per sex	19.2	4.56	6/10
4	5 per sex	4.36	1.29	0/10

LC50	4.04 mg/L/4 hours (males) 3.83 mg/L/4 hours (females)
Signs of Toxicity	Common clinical signs included decreased respiratory rate, laboured respiration, hunched posture, pilo-erection, and wet fur. Frequent instances of increased respiratory rate, noisy respiration and sneezing, occasional instances of ataxia, chromodacryorrhoea, lethargy, prostration, ptosis and red/brown staining around the snout and/or eyes were noted. Isolated occurrences of gasping respiration, coma, dehydration, occasional body tremors and stained head were also noted. Surviving animals of Group 1 appeared normal on Day 6 post-exposure. Surviving animals of Group 2 recovered to appear normal from Days 5-10 post-exposure. Surviving animals of Group 3 recovered to appear normal on Day 8 post-exposure and all animals of Group 4 appeared normal on Day 2 post-exposure.
Effects in Organs	No macroscopic abnormalities were noted at necropsy in animals that survived until the end of the recovery periods, except that 1 male animal of Group 1 and 1 female animal of Group 3 exhibited dark patches on the lungs. The study authors stated that there were no abnormal findings observed in the upper respiratory tract of the treated animals during necropsy. Macroscopic abnormalities were noted at necropsy in animals that were

humanely killed or were found dead during the course of the study, including abnormally dark lungs, dark patches in lungs, dark liver, dark kidneys, abnormally red glandular region in stomach, black contents in stomach, gaseous distension in small intestine and large intestine.

Remarks – Results

All surviving animals of Group 1 exhibited body weight losses on Day 1. Two males and 3 female animals exhibited further body weight losses from Days 1-3. Body weight gains were then noted in all surviving animals during the remainder of the recovery period. Six out of 7 surviving animals of Group 2 exhibited body weight losses on Day 1. Three males and 1 female animal exhibited further body weight losses from Days 1-3. Body weight gains were then noted in all surviving animals during the remainder of the recovery period. All surviving animals of Group 3 exhibited body weight losses on Day 1. Body weight gains were then noted in all surviving animals during the remainder of the recovery period. Two males and 2 female animals of Group 4 exhibited body weight losses on Day 1. Body weight gains were then noted in all animals during the remainder of the recovery period.

It was considered by the study authors that deaths noted during the study may have been mainly attributable to systemic toxicity, based on the observations during the study and at necropsy.

CONCLUSION

The notified chemical is harmful via inhalation.

TEST FACILITY

Harlan (2015a)

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

TEST SUBSTANCE

Notified chemical

METHOD

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

Vehicle

None

Remarks – Method

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

The test substance (10 µL) was applied to the tissues in triplicate. Following an exposure period of 15 minutes (at room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 42 hours.

Negative and positive controls were run in parallel with the test substance:

- Negative control: Dulbecco's phosphate buffered saline
- Positive control: 5% sodium dodecyl sulphate in distilled water

RESULTS

Test Material	*Mean OD_{562} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	0.868	100	1.3
Test substance	0.024	8.3	2.8
Positive control	0.093	10.7	1.4

OD = optical density; SD = standard deviation

Remarks – Results

The relative mean viability of the tissues treated with the test substance was ≤ 50% (predicted as irritant according to the criteria).

The positive and negative controls gave satisfactory results, confirming the

validities of the test systems.

CONCLUSION Based on the mean tissue viability of ≤ 50%, the notified chemical should be classified for skin irritation (Category 2) according to the GHS criteria.

TEST FACILITY Harlan (2015b)

B.5. Skin Corrosion – *In Vitro* Reconstructed Human Epidermis Model

TEST SUBSTANCE Notified chemical

METHOD OECD TG 431 *In vitro* Skin Corrosion – Human Skin Model Test
EPISKIN™ Reconstructed Human Epidermis Model

Vehicle None

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

The test substance (50 µL) was applied to the tissues in duplicate. Following exposure periods of 3, 60 and 240 minutes (room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 3 hours.

Negative and positive controls were run in parallel with the test substance:
- Negative control: 0.9% sodium chloride in water
- Positive control: glacial acetic acid

RESULTS

Test material	*Mean OD_{562} of duplicate tissues*	*Relative mean Viability (%)*
Negative control (3 min exposure)	1.125	100*
Negative control (60 min exposure)	1.117	100*
Negative control (240 min exposure)	0.926	100*
Test substance (3 min exposure)	1.258	111.8
Test substance (60 min exposure)	1.202	107.6
Test substance (240 min exposure)	1.215	131.2
Positive control (240 min exposure)	0.046	5.0

OD = optical density; SD = standard deviation
* The mean viability of the negative control tissues was set as 100%

Remarks – Results The relative mean viability of the tissues treated with the test substance for 240 minutes was ≥ 35% (predicted as non-corrosive according to the criteria).

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

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

Based on the relative mean tissue viability of ≥ 35%, the notified chemical is not classified as corrosive (Category 1) according to the GHS criteria.

TEST FACILITY Harlan (2015c)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

Vehicle	None
Remarks – Method	No significant deviations of protocol were noted. Negative and positive controls were run in parallel with the test substance: - Negative control: 0.9% w/v sodium chloride in water - Positive control: ethanol

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues*	*Mean Permeabilities of Triplicate Tissues*	*IVIS*
Vehicle control	1.3	0.037	1.9
*Test substance**	37.7	2.035	68.2
*Positive control**	28.3	1.418	49.6

IVIS = *in vitro* irritancy score
*Corrected for background values

Remarks – Results	The test substance resulted in an IVIS of 68.2 (classified as Category 1; Causes serious eye damage according to the GHS criteria).
CONCLUSION	The notified chemical causes serious eye damage under the conditions of the test.
TEST FACILITY	Harlan (2015d)

B.7. Skin Sensitisation – Guinea Pig Maximisation Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Magnusson and Kligman
Species/Strain	Guinea pig/Dunkin Hartley
PRELIMINARY STUDY	Maximum non-irritating concentration: Intradermal: 10% Topical: 20%
MAIN STUDY	
Number of Animals	Test Group: 10 F (each test) Control Group: 5 F (each test)
Vehicle	Olive oil (intradermal injection) and liquid paraffin (topical administration)
Positive Control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
INDUCTION PHASE	Induction concentration: Intradermal: 10% Topical: 50%
Signs of Irritation	*First main test*: In the negative control group, no irritation reactions were noted after the 1st induction (intradermal) and dryness was noted in 3/5 animals after 2nd induction (topical). In the treated group, discrete erythema was noted in 2/10 animals after the 1st induction (intradermal) and dryness was noted in 10/10 animals after 2nd induction (topical). *Second main test*: In the negative control group, no irritation reactions were noted after the 1st induction (intradermal) and dryness in 2/5 animals and scabs in 3/5 animals were noted after 2nd induction (topical). In the treated group, discrete erythema was noted in 3/10 animals after the 1st induction (intradermal) and dryness in 4/10 animals and scabs in 6/10 animals were noted after 2nd induction (topical).
CHALLENGE PHASE	
1st Challenge	Topical: 20% (each main test)
2nd Challenge	Topical: 10% (1st main test)
Remarks – Method	No significant protocol deviations. Two main tests were conducted.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st Challenge		*2nd Challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group (1st test)	1st challenge: 20% 2nd challenge: 10%	4/10	0/10	2/10	0/10
Negative Control Group (1st test)	1st challenge: 20% 2nd challenge: 10%	1/5	0/5	0/5	0/5
Test Group (2nd test)	20%	0/10	0/10	-	-
Negative Control Group (2nd test)	20%	0/5	0/5	-	-

Remarks – Results

No mortalities were noted in main tests. The mean body weight and body weight gain were not affected.

First main test:
In the negative control group, discrete erythema was noted in 1/5 animals at 24 hours after the challenge phase. No irritation reactions were noted at 48 hours.

In the treated group, discrete erythema was noted in 4/10 animals at 24 hours after the 1st challenge phase. No skin reactions were noted at 48 hours except dryness of the skin in 2 animals. In the second challenge at 10% concentration discrete erythema was noted in 2/10 animals in the treatment group and no animals in the control.

Discrete erythema was noted on the treated area with the vehicle (liquid paraffin) in animals from the treated group after the first challenge phase (1/10) and after the second challenge phase (1/10). It was considered by the study authors that the vehicle (liquid paraffin) had some impact on the results and the second main test was therefore conducted.

Second main test:
No skin reactions were noted after the challenge in the vehicle control group and the treated group.

CONCLUSION

There was no evidence indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY

Phycher (2016)

B.8. Repeat Dose Oral Toxicity with Reproduction/Developmental Toxicity Screening – Rat

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

Species/Strain: Rat/Crl:CD(SD)
Route of Administration: Oral – gavage
Exposure Information: Total exposure days:
Main study males: 2 weeks pre-pairing, throughout pairing up to necropsy. A minimum of 6 weeks treatment in total.
Main study females: 2 weeks before pairing, throughout pairing and gestation until Day 7 of post-partum.
Treatment toxicity phase females (not paired): at least 6 weeks
Recovery phase animals: at least 6 weeks treatment, followed by at least 14 days recovery
Dose regimen: 7/7 days per week
Post-exposure observation period: 14 days

Vehicle	Corn oil
Remarks – Method	No significant protocol deviations were noted. The dose selection for the main study was based on the results in a 2-week preliminary study in which treatment at 1000 mg/kg bw/day resulted in all animals being euthanised after 3 doses due to poor clinical conditions and treatment at 300 mg/kg bw/day resulted in all female animals being euthanised on Day 6 and 1 male animal being euthanised on Day 13, due to poor conditions. Treatment at 100 mg/kg bw/day was well tolerated for 14 days. The results of this preliminary study also suggested that females were more susceptible to the toxicity of this test substance than males. Female animals in the toxicity phase were not paired and were necropsied at 7 weeks.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 per sex	0	0/10
Low Dose	10 per sex	12	0/10
Mid Dose	10 per sex	35	0/10
High Dose	10 per sex	105	0/10
Control (toxicity phase)	5 female	0	0/10
High Dose (toxicity phase)	5 female	105	0/5
Control Recovery	5 per sex	0	0/5
High Dose Recovery	5 per sex	105	0/5

Mortality and Time to Death

There were no mortalities.

Clinical Observations

No treatment-related clinical signs were noted. Sensory reactivity, grip strength and motor activity were unaffected by treatment.

Overall body weight gain in females dosed at 105 mg/kg bw/day was low in the toxicity phase and during lactation, and was marginally low in all treated females at the commencement of gestation. Body weight gain was not affected in males.

No treatment-related effects on water consumption or food consumption of males, toxicity phase females or females prior to pairing were noted. However, food consumption in all groups of treated females was slightly low during Days 0-6 of gestation, while during lactation food intake was slightly low during Days 1-3 at 35 mg/kg bw/day or Days 1-6 at 105 mg/kg bw/day.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology

Statistically significant changes when compared with the control included; mean cell haemoglobin (95 or 98% respectively) and mean cell volume (94 or 97% respectively) were marginally low and platelet count was low (85 or 88% respectively) in male animals treated at 35 or 105 mg/kg bw/day. Mean reticulocyte count was marginally low (73%), neutrophil (53%), monocyte (56%) and concomitant leucocyte count (74%) were low and prothrombin time was protracted (110%) in animals treated at 105 mg/kg bw/day. Differences in female animals treated at 105 mg/kg bw/day were limited to low reticulocyte count (35%) and marginally low red cell distribution width (91%), when compared with the controls.

In Week 2 of the recovery period, reticulocyte count and red cell distribution width were high in animals previously treated at 105 mg/kg bw/day (males 121% and 108%; females 150% and 104%, respectively). Other differences from the controls that showed statistical significance were marginal in nature and seen in female animals only; haematocrit was low (94%), haemoglobin was low (95%) and mean cell volume was low (96%). Mean cell haemoglobin concentration was marginally high (102%).

Blood chemistry

When compared with the controls, statistically significant findings included high alkaline phosphatase activity in male animals treated at 105 mg/kg bw/day (131%) and female animals treated at 105 mg/kg/bw day (156%), bile acid concentration was markedly high in male and female animals treated at 105 mg/kg bw/day (316 or 498%

respectively), triglyceride concentration was low in male animals treated at 105 mg/kg bw/day (27%) and female animals at 105 mg/kg bw/day (48%), and total protein and albumin concentrations were marginally low in both sexes treated at 105 mg/kg bw/day (males 90 and 94%; females 82 and 85% respectively). In addition, calcium concentration was also low in males and females at 105 mg/kg bw/day (both approximately 92%).

Other statistically significant differences from the controls noted in male animals included high alanine amino-transferase (134%) and aspartate amino-transferase (129%) activities, high urea/blood urea nitrogen (136%) and marginally low phosphorous concentration (90%) and high albumin/globulin ratio (113%) at 105 mg/kg/day. In female animals marginally low sodium concentrations (98%) and marginally high potassium concentrations (119%) were observed.

Creatinine concentration was high in male animals previously treated at 105 mg/kg bw/day (123%), during the Week 2 of recovery from treatment.

Alanine amino-transferase activity was low in animals treated at 35 or 105 mg/kg bw/day (72 or 75%) and calcium and protein concentrations were low in animals treated at 105 mg/kg bw/day (90%) on Day 8 of lactation, when compared with the controls.

Urinalysis

There were no statistically significant changes seen in urinalysis parameters for any of the treated groups.

Changes observed in haematology, blood chemistry and urinalysis parameters following treatment were considered by the study authors as non-adverse due to the lack of any macroscopic or microscopic histopathological effects.

Effects in Organs

Adjusted mean seminal vesicle weight was low in male animals, following 6 weeks of treatment at 12, 35 or 105 mg/kg/bw day (86, 86 or 83% respectively) and was high in animals previously treated at 105 mg/kg bw/day (114%), following 2 weeks recovery from treatment. Mean adjusted ovary weight in toxicity phase female animals treated at 105 mg/kg bw/day was low (90%). Low adjusted spleen weight (80% of Control) was noted on Day 8 of lactation in female animals treated at 105 mg/kg bw/day. No treatment-related adverse findings in macropathology and micropathology were noted and organ weights were not adversely affected.

Reproductive performance

Oestrous cycles, pre-coital interval, mating performance and fertility were considered by the study authors to be unaffected by treatment. One female (out of 10) treated at 105 mg/kg/bw day was acyclic and two animals treated at 12 and 105 mg/kg bw/day respectively had irregular cycles. Gestation length and gestation index were unaffected by treatment, with all animals littering within 22-23.5 days of mating.

Clinical examinations in F1 pups

The mean post implantation survival index (90.6% vs 95.0% for control) and mean live litter sizes (12.4 vs 14.7-14.9 for control) were slightly low for the 105 mg/kg bw/day dose group. The mean bodyweights and changes of male and female offspring on Day 1 of age were not affected by treatment at 105 mg/kg bw/day but the subsequent growth of the female offspring at this dose was slightly lower (85%) than the controls during days 4-7 after birth although there was no statistically significant reduction in bodyweight change over the combined 7 day period after birth. There was no effect of treatment at 35 or 12 mg/kg bw/day on litter size, offspring survival or offspring growth.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 105 mg/kg bw/day (the highest dose tested) by the study authors, based on no treatment-related adverse findings were noted at all doses tested.

The reproductive/developmental NOAEL was established as 35 mg/kg bw/day, based on lower mean post implantation survival index, lower mean live litter sizes, and slower growth of the offspring noted at the highest dose level (105 mg/kg bw/day).

TEST FACILITY Envigo (2015b)

B.9. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test Pre incubation procedure
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 0.5-1500 µg/plate b) Without metabolic activation: 0.5-1500 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks – Method	A dose range-finding study was carried out at 1.5–5000 µg/mL to select the concentrations for the main test. Positive controls: With metabolic activation: 2-aminoanthracene (WP2uvrA, TA100, TA1535, TA1537); benzo(a)pyrene (TA98) Without metabolic activation: *N*-Ethyl-*N'*-nitro-*N*-nitrosoguanidine (WP2uvrA, TA100, TA1535); 9-aminoacridine (TA1937); 4-nitroquinoline-*N*-oxide (TA98)

RESULTS

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

Remarks – Results	There were two isolated statistically significant increases in the mean number of revertants in the range finding test. One without metabolic activation (WP2urvA, 1.5 µg, 160% of control) and one with metabolic activation (TA100, 50 µg, 122% of control). Both increases were within historical control levels for the laboratory and had no dose response relationship attached and therefore were not considered to be toxicologically significant by the study authors. No other significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, at any test concentration, either with or without metabolic activation.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Harlan (2015e)

B.10. Genotoxicity – *In Vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Human
Cell Type/Cell Line	Peripheral lymphocytes
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks – Method	The dose selection for the main tests was based on toxicity and precipitation noted in the range finding study carried out at 6.38 –

1632.6 µg/mL.

Vehicle control and positive controls (mitomycin C and cyclophosphamide) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 12.5, 25, 50, 100*, 150*, 200*, 250*, 300	4 h	24 h
Test 2	0*, 6.25*, 12.5*, 25*, 50*, 66.7*, 83.4, 100, 125, 150	24 h	24 h
Present			
Test 1	0*, 12.5, 25, 50, 100, 150, 200*, 250*, 300*	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	≥ 408.15	≥ 250	> 300	negative
Test 2	≥ 204.08	≥ 66.7	> 150	negative
Present				
Test 1	≥ 408.15	> 300	> 300	negative

* Based on mitotic index ≤ 50%

Remarks – Results

In both main tests, no statistically significant increases in the frequency of cells with structural or numerical chromosome aberrations were observed in the presence or absence of metabolic activation.

The positive and negative controls gave a satisfactory response 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

Harlan (2015f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)

Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	N/A
Analytical Monitoring	BOD and HPLC
Remarks – Method	As per OECD test guideline 301C. No variations were noted.

RESULTS

Test Substance			*Aniline*	
Day	*% Degradation (BOD)*	*% Degradation (HPLC)*	*Day*	*% Degradation*
7	0 (-1)		7	87
14	0 (-3)		14	94
21	0 (-3)			
28	0 (-3)	0 (-1)		

Remarks – Results: All validity criteria were met. Difference between replicates was 5%. The reference substance was degraded by 87% after 7 days and 94% after 14 days. The BOD of the control sample was 27 mg/L after 28 days.

CONCLUSION: The notified chemical is not biodegradable.

TEST FACILITY: CERI (2016)

C.1.2. Bioaccumulation

TEST SUBSTANCE: Notified Chemical

METHOD: OECD TG 305-I Bioconcentration: Flow-through Fish Test
EC Directive 98/73/EC C.13 Bioconcentration: Flow-Through Fish Test

Species	
Exposure Period	Exposure: 28 days Depuration: N/A
Auxiliary Solvent	N/A
Concentration Range	Nominal: 50 µg/L (High exposure level) 5 µg/L (Low exposure level) Actual: 48.2 µg/L (High exposure level) 4.92 µg/L (Low exposure level)
Analytical Monitoring	GC-MS
Remarks – Method	As per OECD test guidelines, with the following options chosen No depuration period was included in this study. The bioconcentration factor was calculated based on the following calculation rather than the ratio between exposure and depuration concentrations: $BCF = C_f / C_w$ Where: C_f is the concentration of the test item in test fish (minus the average concentration in control fish) and C_w is the concentration of the test item in the test water during the uptake phase.

RESULTS

Bioconcentration Factor	38-48 L/kg
Remarks – Results	All validity criteria were met. Water temperature was maintained at 25°C ± 2°C, dissolved oxygen content was maintained above 60% and the test item concentration was maintained at ±20% of the mean measured values and was below the limit of water solubility. No mortality or adverse effects were observed in the control test group.

CONCLUSION The notified chemical is not expected to be bioaccumulative.

TEST FACILITY CERI (2018)

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
EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish – semi-static

Species	
Exposure Period	96 hours
Auxiliary Solvent	N/A
Water Hardness	99.1 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	As per OECD test guidelines. No variations were noted, Test solutions were renewed at 48 hours. A positive control was also conducted using potassium dichromate (details not recorded).

RESULTS

Concentration (mg/L)		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	0	10	0	0	0	0	0
7.00	6.40	10	0	0	0	0	0
8.33	8.00	10	0	0	0	0	0
9.90	9.10	10	0	0	0	0	0
11.8	10.8	10	0	1	2	2	3
14.0	12.4	10	1	5	7	7	8

LC50	12.7 mg/L at 96 hours calculated using probit.
NOEC (or LOEC)	9.10 mg/L at 96 hours
Remarks – Results	Probit was used to calculate the LC50 value, however typically 2 partial responses are required to accurately determine this value. All validity criteria were met. Dissolved oxygen was maintained above 60% and concentration of the test substance was maintained above 80% of the nominal concentration. Reference test concluded a 24hr EC50 value of 230 mg/L

CONCLUSION The notified chemical is harmful to fish.

TEST FACILITY GDCM (2015)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction

	Test – semi-static EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia – semi-static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	N/A
Water Hardness	160-180 mg $CaCO_3$/L
Analytical Monitoring	LC-MS
Remarks – Method	As per OECD test guidelines. No deviations were noted, solutions replaced daily. A reference test was also conducted using potassium dichromate approximately 5 months prior to the current study.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
Control	0	20	0	0
0.625	0.64	20	0	0
1.25	1.35	20	0	0
2.50	2.54	20	1	2
5	5.05	20	3	8
10	10.2	20	14	20

LC50	5.71 mg/L at 48 hours calculated by sigmoidal dose-response regression.
NOEC (or LOEC)	1.35 mg/L at 48 hours
Remarks – Results	All validity criteria were met. Dissolved oxygen concentration was >7.90 mg/L in all test vessels and control vessels. Reference test concluded a 24hr EC50 value of 1.88mg/L.

CONCLUSION The notified chemical is toxic to daphnia.

TEST FACILITY DR.U. Noack-Laboratorien (2015c)

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: 1.70 – 8.61 mg/L Actual: 1.03 – 8.75 mg/L (Geometric mean of daily measurments).
Auxiliary Solvent	N/A
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	LC-MS
Remarks – Method	As per OECD test guidelines. No deviations were noted. A reference test was conducted using potassium dichromate approximately 5 months prior to the current study.

RESULTS

Growth rate		*Yield*	
ErC50 (mg/L at 72 h)	*NOEC (mg/L)*	*EyC50 (mg/L at 72 h)*	*NOEC (mg/L)*
6.40 (6.27 – 6.53	< 1.03	3.86 (3.55 – 4.15)	< 1.03

Remarks – Results	All Validity criteria were met. An 81-fold growth rate (1.46 specific growth rate) was observed in the control cultures. The coefficients of variation were 25.2% in the control cultures and 0.96 in the replicate

	control cultures. The reference test concluded a 72 hr ErC50 value of 0.613 and EyC50 value of 0.281.
CONCLUSION	The notified chemical is toxic to algae.
TEST FACILITY	DR.U. Noack-Laboratorien (2016)

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