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March 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Furan, 5-(hexyloxy)tetrahydro-2,2-dimethyl- (INCI Name: Hexyloxy Dimethyltetrahydrofuran)

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/1956	International Flavours and Fragrances (Australia) Pty Ltd	Furan, 5-(hexyloxy)tetrahydro-2,2-dimethyl- (INCI Name: Hexyloxy Dimethyltetrahydrofuran)	Yes	≤ 1 tonne per annum	Ingredient in cosmetic and household products

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is 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 recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 4)	H227 – Combustible liquid
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
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 2	H401 Toxic to aquatic life
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 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:
  - Flammable Liquids (Category 4): H227 – Combustible liquid
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - 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 and the intended use/exposure scenario.

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

- Due to the flammable properties of the notified chemical, the notifier should consider their obligations under the Australian Dangerous Goods Code.

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 allergic skin reactions.

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:
  - Enclosed, automated processes, 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

- 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, impervious gloves, goggles

  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.

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.

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 an inert, non-combustible absorbent material and subsequent safe disposal..

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 1.5% in fine fragrances and leave-on cosmetic products, 0.8% in non-aerosol deodorants, 5% in rinse-off cosmetic products, 5% in hairspray and air care products and 2.5% in household products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from an ingredient in cosmetic and household products 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.

(Material) 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)
International Flavours and Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH and dissociation constant.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
Canada (NDSL) 2016
China
E.U. (REACH)
Philippines
U.S.A. (TSCA) 2016

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Rejuvenix

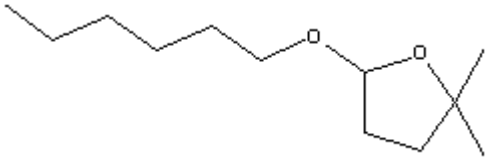
CAS NUMBER
1497420-94-6

CHEMICAL NAME
Furan, 5-(hexyloxy)tetrahydro-2,2-dimethyl-

OTHER NAME(S)
Hexyloxy Dimethyltetrahydrofuran (INCI Name)
5-(Hexyloxy)-2,2-dimethyltetrahydrofuran
5-(Hexyloxy)tetrahyrdo-2,2-dimethylfuran
FRET 09-0035
IFF 09-0035
Hexyloxy DMTF
Hexyloxy DMF

MOLECULAR FORMULA
$C_{12}H_{24}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
200.32 Da

ANALYTICAL DATA
Reference NMR, IR, GC, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
99.7%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None.

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None.

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid

Property	Value	Data Source/Justification
Melting Point	< -80 °C	Measured
Boiling Point	224 °C at 104.2 kPa	Measured
Density	875 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.1 × 10^{-2} kPa at 25 °C	Measured
Water Solubility	0.0640 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 5.6 at 35 °C (HPLC method) log Pow = 3.8 at 20 °C (Shake-flask method)	Measured
Surface Tension	59.7 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 4.43 at 35 °C	Measured
Dissociation Constant	Not determined	The notified chemical does not contain any functional groups that are expected to dissociate in water.
Flash Point	87 °C	Measured
Flammability	Not determined.	Not required based on flash point
Autoignition Temperature	195 °C	Measured
Explosive Properties	Not explosive	Estimated
Oxidising Properties	Not oxidising	Estimated

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 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 recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 4)	H227 – 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 either in neat form for formulation into fragrance preparations and end-use products, as a component of fragrance preparations (at concentrations ≤ 10%) to be blended into end-use products, or as a component of end-use products (at concentrations ≤ 5%).

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
Melbourne.

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours and Fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical may be imported into Australia in its neat form or as a component of fragrance preparations (at concentrations ≤ 10%) in 55 gallon polypropylene-lined steel drums. End-use products containing the notified chemical (at concentrations ≤ 5%) will be in packaging suitable for retail sale

USE
The notified chemical will be used as an ingredient in cosmetic and household products. The concentration of the notified chemical in final consumer products will vary but the proposed usage concentrations will not exceed 5%.

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging of the notified chemical will occur at the notifier's facility. Imported products containing the notified chemical (at concentrations ≤ 100%) will be stored at this facility until they are transported to customer facilities (in original importation packaging) or for reformulation into consumer products.

Reformulation
At the customer facilities, the notified chemical (in neat form or within fragrance preparations at a concentration of ≤ 10%) will be formulated into end-use products. The reformulation procedure will likely vary depending on the nature of the formulated products, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and use closed systems with adequate ventilation, followed by automated filling of the reformulated products into containers of various sizes.

End-use
Household products
Household products containing the notified chemical (≤ 5% concentration) may be used by consumers and professional workers (such as cleaners). The products may be used in either closed systems or open manual processes including rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 5% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be 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	-	-
Blending, packaging and maintenance workers	1 - 4	250
Quality Control workers	1	250
Beauty care and Cleaning workers	8	250

Transport and storage
Transport and storage workers may come into contact with the notified chemical in its neat form, as a component of fragrance preparations (at concentrations ≤ 10%) or as a component of end-use products (at concentrations ≤ 5%) only in the event of accidental rupture of the drum containers.

At the notifier's facility, the primary work activity undertaken by transport and warehouse workers will include handling, loading and off-loading of drums or cartons containing the notified chemical at ≤ 100% concentration. Exposures of these workers will be limited to situations involving cleaning up from a spill or leaking drum. If such an event occurs, workers may be exposed through dermal and ocular contact. Inhalation exposure to the notified chemical is not expected based on the low vapour pressure of the chemical at room temperature. The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective coveralls, chemical resistant gloves and safety glasses.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during weighing and transfer stages, blending, quality control analysis, packaging of materials and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of adequate local ventilation, and through the use of PPE such as coveralls, goggles and impervious gloves.

Beauty care and cleaning professionals
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 (e.g. hair dressers, 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 is also possible. Such professionals may use PPE to minimise repeated exposure, but the use is not always expected. However, the notifier states that good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the finished 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 wide range of cosmetic and household products (at ≤ 5% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if the products are applied by spray.

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*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5 mg/L/4 hour; low toxicity
Skin irritation (in vitro) – EpiDerm Human Skin Model	non-corrosive
Skin irritation (in vitro) – EpiSkin Human Skin Model	irritating
Eye irritation (in vitro) – Bovine Corneal Opacity and Permeability test	non-corrosive or severely irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (2%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL > 15000 ppm (Males: > 992 mg/kg bw/day; Females: > 1213 mg/kg bw/day)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test in human lymphocytes	non genotoxic
Rat, reproductive and developmental toxicity	NOAEL > 15000 ppm (Males: > 1134 mg/kg bw/day; Females: > 1645 mg/kg bw/day)

Toxicokinetics, metabolism and distribution

No toxicokinetic data on the notified chemical were submitted. For dermal and gastrointestinal absorption, molecular weights below 100 Da are favourable for absorption and molecular weights above 500 Da do not favour absorption (ECHA, 2014). Dermal uptake is likely to be low to moderate if the water solubility is between 1-100 mg/L. Dermal uptake through the epidermis may be limited if the partition coefficient (log P) values are greater than 4, but uptake into the stratum corneum is expected to be high (ECHA, 2014). Gastrointestinal absorption is also likely to be high if the partition coefficient (log P) values are greater than 4. Absorption of the notified chemical through the skin and gastrointestinal tract is expected based on the partition coefficient (5.6), water solubility (64 mg/L) and moderately low molecular weight (200.32 Da).

Acute toxicity

The notified chemical is of low acute oral, dermal and inhalation toxicity based on studies conducted in rats.

Irritation and sensitisation

The notified chemical was irritating to the skin but not corrosive based on *in vitro* studies. The notified chemical was not corrosive or severely irritating to the eye based on an *in vitro* study conducted on bovine corneas, but was slightly irritating to the eye based on an acute study conducted on rabbits. However, the level of irritation was insufficient for classification under the GHS

The notified chemical was positive in a local lymph node assay with a concentration of approximately 71.1% corresponding to a Stimulation Index of 3 (also referred to as EC_3). In a human repeated-insult patch study (at 2% concentration) the notified chemical did not show sensitising effects. Based on these results the notified chemical cannot be excluded from being a weak sensitiser.

Repeated dose toxicity and toxicity for reproduction

In a combined repeated dose (dietary) toxicity study with reproduction/developmental toxicity screening test in rats, the No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established as > 992 mg/kg bw/day for males and > 1213 mg/kg bw/day for females based on absence of adverse effects in animals exposed to the highest dose tested (15,000 ppm). A lower than expected number of pregnant females in the control, low-, mid-, and high-dose groups (with corresponding lower fertility and conception indices) was recorded. However, as no correlating morphological findings were observed in the reproductive organs of males or females and the effect was also observed in the control group, the study authors considered the low number of pregnant females to be unrelated to exposure to the test substance. However, the reproduction/developmental NOAEL in this study could not be determined due to the low number of pregnancies and hence a second study was performed.

In the second study the NOAEL was established as > 1134 mg/kg bw/day for males and > 1645 mg/kg bw/day for females based on absence of parental, reproduction or developmental toxicity in animals exposed to the highest dose tested (15,000 ppm).

Mutagenicity/Genotoxicity
The notified chemical was non-genotoxic in a bacterial reverse mutation assay and in an *in vitro* mammalian chromosome aberration test in cultured peripheral human lymphocytes.

Health hazard classification
Based on the available information, the notified chemical is 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 recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Sensitisation, skin (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Transport and Storage
Workers may experience dermal and accidental ocular exposure to the notified chemical (at ≤ 100% concentration) in the event of a discharge via spill or drum leakage. The use of PPE (e.g. impervious gloves, goggles, coveralls, hard hats and respiratory protection, if necessary) should minimise the potential for exposure. Provided adequate control measures and safe work practices are in place to minimise worker exposure, including PPE, the risk to workers from the notified chemical is not considered to be unreasonable.

Reformulation
Exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during blending operations. The notified chemical is considered to be a sensitiser, a skin irritant and has the potential to cause slight eye irritation effects. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

Provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to workers from use 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. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experience by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health
Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products (containing the notified chemical at ≤ 5% concentration in individual products). The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

The notified chemical is a skin irritant and slightly irritating to the eyes. However, given the low proposed end use concentrations in cosmetic and household products irritation effects are not expected.

The notified chemical is considered to have the potential to cause skin sensitisation. Methods for the quantitative risk assessment of dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using fine fragrances (containing 1.5% notified chemical), or deodorants (containing 0.8% notified chemical) as a worst case scenario of products that may contain the notified chemical, the Consumer Exposure Level (CEL) is estimated to be 56.25 μg/cm^2 for fine fragrances and 60.00 for deodorants (Cadby *et al.*, 2002).

When tested in an LLNA study, the notified chemical was a skin sensitiser with an EC_3 value of 71.1%. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 51.84 μg/cm^2. In this instance, the factors employed included an

interspecies factor (3.16), intraspecies factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of ~300.

For a fine fragrance containing 1.5% notified chemical or deodorants containing 0.8% notified chemical, the AEL < CEL. An AEL equivalent to the CEL may be attained from reducing concentrations of the notified chemical in fine fragrances to ≤ 1.38% or deodorants to 0.69%. Based on the results obtained in the HRIPT study at a concentration of 2%, and the relatively small difference between the proposed CEL and the AEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances or deodorants is not considered to be unreasonable.

Based on the significantly lower expected exposure level from other leave on and rinse-off cosmetic products (containing ≤ 5% notified chemical), and household products (≤ 5% notified chemical), by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 1.5% in fine fragrances and leave-on cosmetic products, ≤ 0.8% in non-aerosol deodorants, ≤ 5% in rinse-off cosmetic products, ≤ 5% in hairspray and air care products and ≤ 2.5% in household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia; therefore there will be no release of the notified chemical to the environment from this activity. The notified chemical will be imported neat, or as a component of fragrance preparations, for reformulation into finished cosmetic and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. Accidental leaks and spills of the product containing the notified chemical are expected to be collected by inert absorbent material and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve in batch blending operations that will be highly automated, and are expected to occur within a fully enclosed system. Therefore, significant release of the notified chemical from this process to the environment is not expected. Wastes containing the notified chemical generated from reformulation include equipment wash water, residues in empty import containers and spilt materials. These will be collected and released to on-site waste water treatment processes, local municipal treatment plant or released directly to sewers in a worst case scenario. Empty import containers are expected to be recycled or disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

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

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical will enter into the sewer system before potential release to surface waters nationwide. The chemical is not readily biodegradable (25% and 40% biodegradation in 28 days with 1 and 3 mg/L respectively) and there is no data available for inherent biodegradability. For details of the environmental fate study, please refer to Appendix C.

Based on its measured adsorption coefficient (log K_{oc} = 4.43) and low water solubility (64 mg/L at 20 °C) the notified chemical is expected to adsorb to sediment or any suspended particulate matter. The notified chemical has high n-octanol/water partition coefficient (log P_{OW} = 5.6) and low molecular weight, indicating a bioaccumulation potential. However, the measured surface tension data (59.7 mN/m at 20 °C) indicates that the notified chemical is expected to behave as a surface active substance and hence significant bioaccumulation is not expected (McWilliams *et al*, 2001). The notified chemical in landfill, soil and sludge is expected to have limited mobility and anticipated to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile from water (vapour pressure = 5.6×10^{-3} kPa at 20 °C, 1.1 x 10^{-2} kPa at 25 °C) and may slowly volatilise to air during sewage treatment. The half-life of the notified chemical in air is calculated to be < 5.1 h, based on reactions with hydroxyl radicals (US EPA, 2011; calculated using AOPWIN v1.92). Therefore, the notified chemical is not expected to persist in the air compartment.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleansing products, it is assumed that 100% of the total import volume of the notified chemical is expected to be released to the sewer treatment plants (STPs) and there is no removal of the notified chemical at STPs. The release is assumed to be nationwide over 365 days per year.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.38 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 12.89 mg/L	Harmful to Fish
Daphnia Toxicity	48 h EC50 = 5.4 mg/L	Toxic to aquatic invertebrates
Algae Toxicity	72 h E_rC50 = 13.78 mg/L	Harmful to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is considered to be toxic to aquatic invertebrates and harmful to both fish and algae. 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 2; Toxic to aquatic life”. Based on the acute toxicity and non-ready

biodegradability of the notified chemical, it is formally classified as “Chronic Category 2; Toxic to aquatic life with long lasting effects” under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the available endpoint for algae (NOEC= 0.33 mg/L for yield). An assessment factor of 100 was used given measured acute endpoints from three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
NOEC (Alga)	0.33 mg/L
Assessment Factor	100
PNEC:	3.30 µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	3.3	**0.18**
Q - Ocean	0.06	3.3	**0.018**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum use volume and assessed use pattern. The notified chemical is not readily biodegradable and due to surface active nature it is not expected to bioaccumulate in aquatic life.

On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point < -80 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	After storage for 19 hours at -21.6 °C the test substance was a liquid. Following storage at -81.6 °C for 19 hours, the test substance was a very viscous liquid.
Test Facility	WIL (2015a)

Boiling Point 224 °C at 104.2 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Differential scanning calorimetry
Test Facility	WIL (2015a)

Density 875 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	Pycnometer
Test Facility	WIL (2015a)

Vapour Pressure 1.1 x 10^{-2} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Isothermal thermogravimetric effusion method.
Test Facility	WIL (2015a)

Water Solubility 0.0640 g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method/Slow-stirring flask Method. The Slow-stirring flask method was used as the notified chemical is volatile.
Test Facility	WIL (2015a)

Partition Coefficient (n-octanol/water) log Pow = 5.6 at 35 °C (HPLC method)
log Pow = 3.8 at 20 °C (Shake-flask method)

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Partition Coefficient of the notified chemical was determined by both HPLC Method and Shake-Flask Method. The result of the HPLC method was found to be much higher than shake flask method. Therefore, considering the worst case scenario assessment was carried out based on the HPLC method data.
Test Facility	WIL (2015a) CRL (2016a)

Surface Tension 59.7 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: 90% Ring method.
Test Facility	WIL (2015a)

Adsorption/Desorption – main test log Koc = 4.43 at 35 °C

Method	OECD TG 121 Adsorption - Desorption Using High Performance Liquid Chromatography (HPLC).
Remarks	The HPLC method using soil-adsorption-reference data was applied for the determination of the adsorption coefficient.
Test Facility	CRL (2016b)

Flash Point 87 °C

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

Autoignition Temperature 195 °C

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

Explosive Properties Not explosive

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	Estimated based on the structure of the notified chemical.
Test Facility	WIL (2015a)

Oxidizing Properties Not oxidising

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks	Estimated based on the structure of the notified chemical.
Test Facility	WIL (2015a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Wistar Crl:WI (Han)
Vehicle	None
Remarks - Method	GLP compliant. No deviations from protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	2,000	0/3
2	3 F	2,000	0/3

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Hunched posture and/or piloerection were observed in all group 1 animals 2 and 4 hours after exposure. All animals in group 2 exhibited hunched posture immediately following exposure and after 2 and 4 hours after exposure. These effects were not observed 24 hours after exposure.
Effects in Organs	No macroscopic abnormalities observed.
Remarks - Results	All animals made the expected bodyweight gains.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	WIL (2015b)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/Wistar Crl:WI (Han)
Vehicle	None
Type of dressing	Occlusive.
Remarks - Method	GLP compliant. No significant deviations from protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	2,000	0/3
2	5 M	2,000	0/5
3	2 F	2,000	0/2

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Scales and/or scabs were seen in the treated area of the animals during the observation period.
Signs of Toxicity - Systemic	Restless behaviour was observed in all females (groups 1 and 3) immediately following exposure. Chromodarcryorrhoea (snout), ptosis (drooping eyelids) and/or lethargy were observed on days 1 and 2.
Effects in Organs	No macroscopic abnormalities observed.

Remarks - Results	All animals made the expected bodyweight gains.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	CRL (2016c)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity. EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation).
Species/Strain	Rat/Wistar Crl:WI (Han)
Vehicle	None
Method of Exposure	Nasal exposure.
Exposure Period	4 hours
Physical Form	Liquid aerosol.
Remarks - Method	GLP compliant. No significant deviations from protocol. Droplet size measured as MMAD 3.8 µm (GSD 1.8) and 3.7 µm (GSD 1.8) during the exposure period.

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	5 M, 5 F	9	5.2 ± 0.1	0/10

LC50	> 5 mg/L/4 hours
Signs of Toxicity	All animals exhibited slow breathing during the exposure period, with lethargy, hunched posture and laboured respiration on day 1. Two females continued to exhibit hunched posture up to day 3.
Effects in Organs	Isolated dark red foci (1/5 males) or several reddish foci (1/5 females) were observed on the thymus. No other macroscopic findings were recorded.
Remarks - Results	A loss in body weight post-exposure was exhibited in 3/5 females on day 2 and 2/5 females on day 4. The three animals regained weight from day 4 to make the expected body weight gains. All male animals lost weight on day 2, but made gains thereafter. All remaining female animals (2/5) made the expected body weight gains with no loss in body weight during the observation period.
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	CRL (2016d)

B.4. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 In vitro Skin Corrosion - Human Skin Model Test EC Council Regulation No 440/2008 B.40 BIS. In vitro Skin Corrosion - Human Skin Model Test EpiDerm (EPI-200)
Vehicle	None.
Remarks - Method	GLP compliant. No significant deviations from protocol.

Negative control: Milli-Q water.
Positive control: Potassium hydroxide.

RESULTS

Test material	Mean OD_{570} of triplicate tissues (± SD)		Relative mean Viability (%)	
	3 min exposure	1 hour exposure	3 min exposure	1 hour exposure
Negative control	2.008 (± 0.012)	1.866 (± 0.056)	100	100
Test substance	1.678 (± 0.157)	1.889 (± 0.016)	84	101
Positive control	0.178 (± 0.009)	0.234 (± 0.090)	9	13

OD = optical density; SD = standard deviation

Remarks - Results

The maximum inter-tissue variability in viability (between two tissues treated identically) and the maximum difference in percentage between the mean viability of two tissues and one of the two tissues were above the acceptability criteria (43% and 27%) at the 1 hour exposure time. However, as the mean viability was negative (13%), the study authors determined that the deviation had no impact on the outcome of the study, and the positive and negative control results were acceptable.

CONCLUSION

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

TEST FACILITY

WIL (2015c)

B.5. Irritation – skin (in vitro)

TEST SUBSTANCE

Notified chemical

METHOD

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

Vehicle

None.

Remarks - Method

GLP compliant
No deviations from protocol.

Negative control: Phosphate buffered saline.
Positive control: 5% (aq) Sodium dodecyl sulphate.

RESULTS

Test material	Mean OD_{570} of triplicate tissues	Relative mean Viability (%)	SD of relative mean viability
Negative control	1.144	100	-
Test substance	0.081	7.1	0.014
Positive control	0.077	6.7	0.002

OD = optical density; SD = standard deviation

Remarks - Results

The positive and negative control results performed as expected.

The relative mean tissue viability of the test substance compared to the negative control was less than 50%.

CONCLUSION

The notified chemical was irritating to the skin under the conditions of the test.

TEST FACILITY

WIL (2015d)

B.6. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
Vehicle	None.
Remarks - Method	GLP compliant. No deviations from the protocol. Negative control: physiological saline. Positive control: 10% (w/v) Benzalkonium Chloride.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	0.033 (1.155)	0 (0.006)	0 (1.216)
*Test substance**	1.033 (2.309)	0.006 (0.014)	1.067 (2.458)
*Positive control**	85.367 (15.948)	6.199 (0.988)	178.333 (3.007)

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

Remarks - Results	Positive and negative controls performed as expected. The IVIS for the test substance was ≤ 3.
CONCLUSION	The notified chemical was not corrosive or a severe eye irritant under the conditions of the test.
TEST FACILITY	WIL (2015e)

B.7. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Females
Observation Period	7 days
Remarks - Method	GLP compliant. No significant deviations from protocol.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0.7	0.7	1	7 days	0
Conjunctiva: chemosis	0	0.3	0	1	48 hours	0
Conjunctiva: discharge	0	0.7	0	1	72 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results	One hour after exposure, mild redness (3/3 animals, persisting in 2/3 animals for at least 48 hours), chemosis (2/3 animals with recovery at the 24 hour and 48 hour observations) and discharge (2/3 animals, persisting

in one animal for at least 48 hours, with recovery in the second animal at the 24 hour observation) were observed. Mild redness was again observed at the 72 hour observation in the animal which had showed recovery from the effect after 24 hours. No corneal or iridial effect were observed.

Adverse effects had been resolved within 72 hours in 2/3 animals and within 7 days in 1/3 animals.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY WIL (2016a)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/J
Vehicle Acetone/Olive oil (4:1 v/v)
Preliminary study Yes
Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-Hexylcinnamaldehyde.
Remarks - Method GLP compliant.
No deviations from the protocol.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/animal)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5	383	-
25	5	703	1.8
50	5	846	2.2
100	5	1587	4.1

EC3 71.1%
Remarks - Results Animals in the preliminary study exposed to the test substance at 100% exhibited very slight erythema on days 2 and 3.

Animals in the main study did not exhibit any signs of irritation or systemic toxicity. All animals made the expected body weight gains. No macroscopic abnormalities were observed. One animal exposed to the test substance at 100% exhibited enlarged auricular lymph nodes.

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

TEST FACILITY WIL (2015f)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (2% concentration)

METHOD Repeated insult patch test with challenge
Study Design Induction Procedure: patches infused with 0.2 mL test substance were applied 3 times per week on Mondays, Wednesdays and Fridays for a total of 9 applications. Patches were removed after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday).
Rest Period: 14 days
Challenge Procedure: identical patches were applied to naïve sites. Patches

	remained in place for 24 h. Sites were graded at 24 h (patch removal), 48 h and 72 h post-challenge application.
Study Group	86 F, 27 M; age range 19 - 69 years
Vehicle	Ethanol: Diethyl phthalate (25:75)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm × 3.63 cm patch. Compliant with Good Clinical Practice principles. No deviations from the study protocol.

RESULTS

Remarks - Results	104/113 subjects completed the study. Nine subjects discontinued the study (5/9 received no applications, 2/9 received two applications, 1/9 received four applications and 1/9 did not attend the challenge phase) with 8/9 subjects discontinuing for reasons unrelated to the application of the test substance, while the remaining subject discontinued the study due to a pre-sensitisation to several test materials and tape reactions. Of the 1/104 subjects who completed the study was absent for the 72 h observation following the challenge application. However, this subject recorded no reaction 96 h following the challenge application. Of the 104 subjects who completed the study, one exhibited barely perceptible erythema following induction applications 3, 4 and 9 (with dryness recorded following application 9). The remaining test subjects exhibited no visible skin reactions during the induction of challenge phases.

CONCLUSION	The notified chemical (at 2% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2014)

B.10. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. The study also essentially conforms to: OECD TG 421 Reproduction/Developmental Toxicity Screening Test OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/ Crl:WI (Han)
Route of Administration	Oral –diet
Exposure Information	Exposure period - female: 41 – 48 days Exposure period - male: 28 - 29 days Dose regimen: 7 days per week
Vehicle	None
Remarks - Method	GLP compliant. No significant deviations from the protocol. Dose ranging study performed to select dosage concentrations. Functional observation tests were performed on 5 animals/sex/group.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)*	
control	10 M, 10 F	-	-	0/10 M, 0/10 F

low dose	10 M, 10 F	1500	Pre-mating: 111 (M), 124 (F) Mating: 102 (M) Post-coitum: 162 (F) Lactation: 278 (F)	0/10 M, 0/10 F
mid dose	10 M, 10 F	5000	Pre-mating: 371 (M), 418 (F) Mating: 357 (M) Post-coitum: 510 (F) Lactation: 851 (F)	0/10 M, 0/10 F
high dose	10 M, 10 F	15000	Pre-mating: 1048 (M), 1213 (F) Mating: 992 (M) Post-coitum: 1470 (F) Lactation: 2413 (F)	0/10 M, 0/10 F

Mortality and Time to Death
There were no unscheduled deaths during the study period.

Clinical Observations
In the last days of lactation 1/10 females in the mid-dose group exhibited hunched posture, pale and lean appearance, and 1/10 females in the high-dose group exhibited piloerection. Alopecia and scabbing were observed in 1/10 males in the high-dose group. No other adverse effects were observed and the study authors considered these effects to be unrelated to the test item.

Animals in the control, low-, and mid-dose groups made the expected body weight gains. Slightly lower body weight gains in males and slight body weight loss in females were observed in the high-dose group during the first week of exposure. These animals then exhibited body weight gains similar to control animals.

Lower food consumption was recorded in females in the mid-dose group (days 9-10 post-coitum) and males (days 1-3, pre-mating) and females (days 1-3, pre-mating and days 5-11 post-coitum) in the high-dose group. No clear dose relationship was established and the authors did not consider lower food consumption to be toxicologically related. One female in the mid-dose group exhibited minimal food intake from Day 22 post-coitum until day 3 of lactation before showing signs of recovery,

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No toxicologically relevant effects were observed on haematology or clinical biochemistry. Males in the low-dose group exhibited statistically significant decreases in red blood cell count, haemoglobin and haematocrit, and a statistically significant increase in mean corpuscular haemoglobin concentration. Statistically significant changes were also observed in urea in males (mid-dose group) and glucose in females (low-dose group). Statistically significant lower prothrombin times were also observed in males in the low- and mid-dose groups. These changes were not considered to be related to exposure to the test substance by the study authors as there were no correlating changes at the organ level, changes were within the control range considered normal for rats of this age and strain or no dose-response relationship was observed.

A high value for bile acid (not statistically significant, but outside the historical control range) in females in the high-dose group was based on the value recorded in one female. This animal also exhibited piloerection during the last days of treatment (see clinical observations). As only one animal exhibited the effect and no other correlating findings at the microscopic level were observed, the study authors did not consider the effect to be relevant to exposure to the test substance.

Effects in Organs
Parental results:
A number of macroscopic changes were observed including a grey/white, soft nodule at the cranial side of the right kidney with correlating nephroblastoma (1/5 males, low dose group; regarded as an incidental finding and not related to treatment by the study authors), smaller testes and epididymides (1/5 males, low dose), reddish discolouration of the mesenteric lymph mode (1/5 females, low dose group), tan coloured, isolated foci on both sides of the clitoral glands (1/5 females low- and mid-dose groups), alopecia on the right cheek (1/5 males, high-dose group), fluid in the uterus (1/5 females, high-dose group) and dark red discolouration on both sides of the mandibular lymph node and exophthalmos on the right side of the eyes (1/5 females, high-dose group).
These macroscopic changes were not considered related to exposure to the test substance by the study authors as the effects were not correlated to other effects or a dose-response relationship was not observed.

An increase in the absolute and relative weights of the liver and kidneys was observed in males (low- and high-dose groups) and females (low-, mid-, and high-dose groups) with males in the mid-dose group exhibiting decreases in the absolute and relative kidney weights. Animals in the high-dose group exhibited statistically higher relative liver weights (males and females) and kidney weights (males).

An increase in the incidence and severity of hyaline droplet accumulation was observed in the kidneys of males in the high-dose group (5/5) (moderate degree) and other groups (2) (minimal degree) including controls. Hyaline droplet accumulation was not accompanied by other degenerative changes of the kidneys apart from one case of minimal granular casts in a high-dose male. Recorded severities remained mild (mostly slight, one rat with moderate degree. Hyaline droplet accumulation is considered to represent $\alpha_{2\mu}$- globulin which is a normal protein specific to male rats and is regarded as a non-adverse finding in this study by the study authors.

The microscopic findings were considered by the study authors to be within the range of background pathology observed in rats of this age and strain and that the alteration in the prevalence, severity, or histologic character of the alterations were not related to exposure to the test substance.

Reproductive results
The study authors reported that the number of pregnant females (7, 6, 9 and 6 in the control, low-, mid- and high-dose groups respectively) was lower than normally expected. This was not considered to be a result of exposure to the test substance by the study authors as mating index, precoital time, and number of corpora lutea and implantation sites were unaffected. In addition, no dose-response relationship or adverse effects in the reproductive organs (normal spermatogenic staging profiles in males and histologic normal cycles in non-pregnant females) were observed.

Developmental results
No toxicologically relevant effects on gestation index and duration, parturition, maternal care and early postnatal pup development (mortality, clinical signs, body weights and macroscopy) were observed.

One pup in the control group was found dead at first litter check. All pups in mid-dose group had a lean appearance on days 4 and 5 of lactation (with corresponding low body weights), which the study authors considered to be secondary to maternal toxicity (see clinical observations). All remaining pups made the expected body weight gains. Incidental clinical symptoms consisted of a pale appearance and scabbing of the snout. No macroscopic abnormalities were observed in any of the pups. The effects were not considered to be related to exposure to the test substance by the study authors as they were within the range considered normal for pups of this age. No other adverse effects on pups were observed.

Remarks – Results
Changes in the kidneys (males) and liver (males and females) of animals in the high-dose group were observed, but not considered to be adverse by the study authors. While no reproductive or developmental toxicity was observed, the number of pregnant females in the control, low-, mid-, and high-dose groups (with corresponding lower fertility and conception indices) was lower than normally expected. However, as no adverse morphological findings in the reproductive organs of males or females were observed, the study authors considered the low number of pregnant females to be unrelated to exposure to the test substance given the effect was observed in the control group, no dose-response relationship was observed and there was an absence of correlating morphological findings (male and female reproductive organs). Nonetheless, the study authors decided that due to the low numbers of pregnant animals it was not possible to derive an reproductive/developmental NOAEL.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as > 15000 ppm (> 992 mg/kg bw/day for males and > 1213 mg/kg bw/day for females) in this study, based on an absence of toxicity at the maximum dose tested.

TEST FACILITY WIL (2016b)

B.11. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.

	EC Council Regulation No 440/2008 B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from Aroclor induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 10 – 3,330 µg/plate b) Without metabolic activation: 10 – 5,000 µg/plate
Vehicle	Ethanol
Remarks - Method	GLP compliant. No significant deviations from the protocol. Positive controls: without metabolic activation – sodium azide (TA1535), ICR-191 (TA1537), 2-nitrofluorene (TA98), methylmethanesulfonate (TA100) and 4-nitroquinoline N-oxide (WP2uvrA); with metabolic activation – 2-aminoanthracene.

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	≥ 333	> 3,330	negative
Test 2		≥ 3330	> 5,000	negative
Present				
Test 1	> 5,000	≥ 3330	> 3,330	negative
Test 2		≥ 3330	> 5,000	negative

Remarks - Results	A reduction in the bacterial lawn was noted at > 333 and > 1000 µg/plate in the absence and presence of metabolic activation respectively. No reduction in the background lawn was observed for *E.coli* strains. No significant dose-related increase in the number of revertants, in the presence or absence of metabolic activation was observed. Positive and negative controls performed as expected.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	WIL (2014a)

B.12. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human
Cell Type/Cell Line	Lymphocyte
Metabolic Activation System	S9 fraction from phenobarbital/β-naphthoflavone induced rat liver.
Vehicle	Ethanol
Remarks - Method	GLP compliant. No significant deviations from the protocol. Positive controls: without metabolic activation – mitomycin C; with metabolic activation – cyclophosphamide.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	50*, 100*, 130*, 160, 200, 230, 260, 300	3 h	24 h

Test 2a	30, 50*, 70*, 100*, 130, 160, 200, 230	24 h	24 h
Test 2b	30*, 50, 70, 100*, 130*, 160, 200, 230	48 h	48 h
Present			
Test 1	50, 100*, 130*, 160*, 200, 230, 260, 300	3 h	24 h
Test 2a	30, 50, 70, 100, 130, 160, 200, 230	3 h	48 h
Test 2b	30*, 100, 130*, 160, 170*, 180, 190	3 h	48 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	≥ 333	≥ 130	≥ 260	none
Test 2a		≥ 100	≥ 200	none
Test 2b		≥ 130	≥ 200	none
Present				
Test 1	≥ 333	≥ 160	≥ 260	none
Test 2a		≥ 200	≥ 200	-
Test 2b		≥ 160	≥ 190	none

Remarks - Results

No statistically significant or biologically relevant increase in the number of cells with chromosome aberrations was observed in the presence or absence of metabolic activation.

No suitable dose levels could be selected for scoring of chromosome aberrations in test 2a in the presence of metabolic activation as insufficient toxicity was observed at 160 μg/mL (36%) and excessive toxicity was observed at 200 μg/mL (86%). The experiment was repeated in test 2b.

No increase in the number of polyploid cells and cells with endoreduplicated chromosomes were observed in the presence or absence of metabolic activation under the conditions of test 1 and 2.

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

WIL (2014b)

B.13. Toxicity to reproduction/development

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 421 Reproduction/Developmental Toxicity Screening Test

Species/Strain: Rat/Crl:WI(Han)

Route of Administration: Oral – diet

Exposure Information: Exposure period - female: 43 – 46 days
Exposure period - male: 30 days

Vehicle: None

Remarks – Method: GLP compliant
No significant deviations from the protocol.
Doses based on previously performed combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (see B.10.).

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)*	
control	10 M, 10 F	-	-	0/10 M, 0/10 F
low dose	10 M, 10 F	1500	Pre-mating: 160 (M), 159 (F) Mating: 117 (M) Post-coitum: 198 (F) Lactation: 282 (F)	0/10 M, 0/10 F
mid dose	10 M, 10 F	5000	Pre-mating: 486 (M), 535 (F) Mating: 371 (M) Post-coitum: 658 (F) Lactation: 983 (F)	0/10 M, 0/10 F
high dose	10 M, 10 F	15000	Pre-mating: 1519 (M), 1645 (F) Mating: 1134 (M) Post-coitum: 1891 (F) Lactation: 2355 (F)	0/10 M, 0/10 F

Mortality and Time to Death
There were no unscheduled deaths.

Effects on Parental (P) animals:
No toxicologically relevant effects were observed in the clinical appearance, body weight, food consumption, macroscopic examination, weights of the testes and epididymides, or histopathology of the reproductive organs in the parental animals following exposure to the test substance.

Adverse effects including alopecia (2/10 females in the control group), lower body weight gain in males (mid-dose animals throughout exposure period, and high-dose animals during the first week of exposure), lower food consumption in males (mid- and high-dose groups in first week of exposure) and females (mid- and high-dose groups post-coitum) were not considered to be related to exposure to the test substance by the study authors as the effects were transient and did not show a dose-response relationship. Lower food consumption in females in the high-dose group on Day 1 – 2 and Day 3 – 4 of the lactation period, reached statistical significance following correction for body weight on Day 3 – 4. The study authors recorded that for lactation Day 3 – 4 no correction for body weight could be made for 4/10 females as their body weight had not been recorded on lactation Day 4. The study authors concluded that the lower food consumption in the high-dose group was not associated with lower body weight gain, and as such was not of toxicological significance.

One female in mid-dose group exhibited thymus discolouration. However, as no other macroscopic effects were exhibited at necropsy in the remaining animals, the finding was considered to be incidental and not related to exposure to the test substance by the study authors.

The numbers of pregnant females were 9, 8, 9 and 9 (control, low-, mid-, and high-dose groups respectively). No toxicologically relevant effects were observed on the mating, fertility and conception indices, precoital time, numbers of corpora lutea and implantation sites, spermatogenic profiling or histopathology examination of reproductive organs. Low organ weights for testes and epididymides was observed in one male (low-dose group) with correlating macroscopic and microscopic changes, including the absence of a left seminal vesicle. The study authors did not consider this observation to be related to exposure to the test substance as only one male was affected and there were no adverse consequence on his fertility. No cause for the failure to sire or deliver offspring was established for the five couples who did not produce pups (one couple in each of the control, mid- and high-dose groups, and two couples in the low-dose group). Spermatogenic staging profiles were normal for all males examined.

No significant adverse effects were observed on gestation index and duration, parturition or maternal care following exposure to the test substance. Five females (1/5 control, 3/5 mid-, 1/5 high-dose groups) delivered a slightly higher number of pups than the number of implantations and/or corpora lutea. The study authors considered this to be due to normal resorption of these areas.

Effects on 1st Filial Generation (F1)
No significant adverse effects were observed on early postnatal pup development. No pups were found dead at the first litter check although 3/107 and 1/103 (control and mid-dose groups respectively) went missing

(potentially cannibalised). Incidental clinical signs included a pale, blue spot on the abdomen (pup from the mid-dose group that went missing), scabs on the snout (6/100 pups in high-dose group), wound on the hind leg (1/107 pups in control group) and missing tail (1/103 pups in mid-dose group). The study authors did not consider the missing pups or clinical signs to be toxicologically relevant as a dose-response relationship was not observed and the incidence of these effects was within the range considered normal for pups of this age.

The body weights of the pups were as expected and no macroscopic abnormalities were observed.

Remarks - Results
No parental, reproduction or developmental toxicity was observed following exposure to the test substance.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as > 15000 ppm (> 1134 mg/kg bw/day for males and > 1645 mg/kg bw/day for females) in this study, based on an absence of toxicity at the maximum dose tested.

TEST FACILITY WIL (2016c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Toxicity control was conducted in parallel and found to be 40% biodegradable which indicates non-inhibitory nature of the test substance (greater than 25%, OECD).

RESULTS

Test substance			*Sodium acetate*	
Day	*Test substance Nominal concentration (mg/L)*	*% Degradation*	*Day*	*% Degradation*
7	1	0	7	66
	3	3		
14	1	15	14	74
	3	22		
21	1	21	21	ND
	3	32		
28	1	25	28	ND
	3	40		

Remarks - Results	Validity criteria for the test are satisfied. The percentage degradation of the reference compound (sodium acetate) surpassed the threshold level of 60% after 14 days (74%). Therefore, the tests indicate the suitability of the inoculum. After 28 days the test substance was degraded by 25% and 40% for low and high concentration respectively. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 D) guideline.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	WIL (2015g)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static.
Species	Zebrafish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC-MS

Remarks – Method

RESULTS

Concentration mg/L					*Number of Fish*	*Mortality*			
Nominal	*Actual (Geometric average)*					*24 h*	*48 h*	*72 h*	*96 h*
	24 h	*48 h*	*72 h*	*96 h*					
Blank-Control					7	0	0	0	0
12.0	6.14	7.43	7.68	8.07	7	0	0	0	0
14.0	8.69	9.70	9.81	9.60	7	0	0	0	0
16.4	7.21	9.36	10.43	11.11	7	0	0	0	1
19.2	10.43	11.93	11.65	12.60	7	0	0	0	1
22.5	11.10	12.03	12.01	13.55	7	0	3	4	6

LC50 12.89 mg/L at 96 hours (95% confidence limit: 12.03 – 14.89 mg/L)

Remarks – Results All the validity criteria were satisfied.

No fish showed any abnormal behaviour (including mortality) in the control group.

No mortality was observed up to 72 h with concentration of 10.43 mg/L.

Initial 14.3% mortality was observed at 96 h with concentration of 11.11 mg/L and increased up to a maximum of 85.7% with concentration of 13.55 mg/L.

At the concentration 9.2 mg/L of the notified chemical 100% mortality was observed within 24 h.

The deviation from nominal to actual test concentration is well above ±20%. Therefore, according to the OECD test guideline measured concentration (geometric average) was used.

CONCLUSION The notified chemical is harmful to fish

TEST FACILITY Suzhou (2016)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test –Static.

Species *Daphnia magna*

Exposure Period 48 hours

Auxiliary Solvent None

Water Hardness 180 mg $CaCO_3$/L

Analytical Monitoring GC

Remarks - Method The test was conducted according to the above test guideline without significant deviation from the protocol.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Blank-Control	-	20	0	0
1.74	1.43	20	0	0
3.35	3.26	20	0	0
9.49	8.10	20	2	20
20.0	17.8	20	18	20
31.8	33.4	20	20	20

LC50 5.4 mg/L at 48 hours (95% confidence limit: 3.3 - 8.8 mg/L)

Remarks - Results All validity criteria were satisfied.

The nominal concentration of the test solution was taken from the measured concentration of the test solution at 0 h.

The measured concentration of the test solution after 48 h was found to be within the range of 84-105%. Based on this the final result was calculated on the average measured concentration 1.6, 3.3, 8.8, 1.9 and 33 mg/L.

CONCLUSION The notified chemical is toxic to aquatic invertebrate

TEST FACILITY WIL (2015h)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test- static.

Species *Pseudokirchneriella subcapitata*

Exposure Period 72 hours

Concentration Range Actual: 0.52, 1.6, 5.6, 18 and 60 mg/L

Auxiliary Solvent None

Water Hardness 24 mg $CaCO_3$/L

Analytical Monitoring GC

Remarks - Method The test was conducted according to the above test guideline without significant deviation from the protocol.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
7.73	0.33	13.78 (95% confident limit: not determined)	0.33

Remarks - Results All validity criteria were satisfied.

A distinct concentration decrease was observed throughout the test.

The deviation from nominal to actual test concentration is above ± 20%. The deviation from the nominal or measured initial concentration was not within the range of ± 20%, analysis of the results should be based on geometric mean concentration, instead a time weighted average was used.

Therefore, the result may not reflect the actual toxicity level of the notified chemical toward the growth of algae and hence the results should be

	treated with caution.
CONCLUSION	The notified chemicals is toxic to algae
TEST FACILITY	WIL (2015i)

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