File No: LTD/1999

February 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4,8-Cyclododecadien-1-one

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/1999	Firmenich Ltd	4,8-Cyclododecadien-1-one	No	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

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

Hazard classification	*Hazard statement*
Acute Category 3	H402 - Harmful to aquatic life

Human health risk assessment
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

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:
  - Adequate 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:
  - Avoid contact with eyes

- No specific personal protective equipment is required for the safe use of the notified chemical itself. However, these should be selected on the basis of all ingredients in the formulation.

- 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.

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

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.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection 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 3% in leave-on and rinse-off cosmetics, 5% in fine fragrances, 3% in household products, 5% in instant action air fresheners and 10% in other types of 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 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 claimed exempt from publication: other names, analytical data, degree of purity, impurities, additives/adjuvants and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for all physical-chemical and toxicological/ecotoxicological endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Japan (2016)

2. IDENTITY OF CHEMICAL

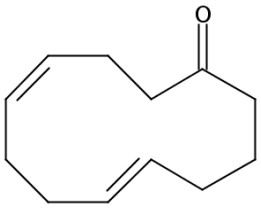
MARKETING NAME(S)
4,8-Cyclododecadien-1-one

CAS NUMBER
15229-79-5

CHEMICAL NAME
4,8-Cyclododecadien-1-one

MOLECULAR FORMULA
$C_{12}H_{18}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
178.27 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	-11 °C (melting) at 101.3 kPa -30 – -33 °C (freezing) at 101.3 kPa	Measured
Boiling Point	250 – 255 °C at 101.3 kPa	Measured
Density	973.5 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.26 × 10^{-3} kPa at 20 °C	Measured
Water Solubility	0.0486 – 0.166 g/L at 20°C	Measured
Hydrolysis as a Function of pH	Hydrolytically stable at pH 2 – 12	Measured
Partition Coefficient (n-octanol/water)	log P_{ow} = 3.48 – 3.53 at 23 °C	Measured
Surface Tension	53.59 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.4 – 2.5 at 23.6 °C	Measured
Dissociation Constant	Not determined	Does not contain readily dissociable functionality
Flash Point	119 °C at 101.1 kPa	Measured
Flammability	Not determined	Not expected to be highly flammable based on the measured flash point
Autoignition Temperature	260 °C	Measured
Explosive Properties	Not determined	Not expected to have explosive properties based on the chemical structure
Oxidising Properties	Not determined	Not expected to have oxidising properties based on the chemical structure

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

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

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

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 in fragrance formulations (≤ 15% concentration) 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 RECIPIENTS
Firmenich 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 tightly closed lacquered drums of varying sizes: 180, 100, 50, 25, 10 or 5 kg. End-use products will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products at typical final use concentrations of ≤ 0.5% in leave-on/rinse-off cosmetics, ≤ 5% in fine fragrances, ≤ 0.5% in household cleaning products, ≤ 5% in instant action air fresheners and ≤ 10% in other types of air fresheners (use details claimed as Exempt Information).

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

The end-use products containing the notified chemical may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse 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
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 event of accidental rupture of containers. Incidental dermal or ocular exposure to the notified chemical may occur via during the clean-up of accidental spills.

Formulation of end use products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at up to 100% concentration) may occur during weighing and transfer stages, equipment preparation, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of local exhaust ventilation, automated and enclosed systems, including sealed delivery systems and through the use of personal protective equipment (PPE) such as gloves, respirator, eye protection and protective clothing.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at ≤ 10% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hairdressers, workers in beauty salons) or in the cleaning industry. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using 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 at various concentrations. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

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

Cosmetic products (Dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.5	1	0.6109
Face cream	1,540	0.5	1	0.1203
Hand cream	2,160	0.5	1	0.1688
Fragrances	750	5	1	0.5859
Deodorant (non-spray)	1,500	0.5	1	0.1172
Shampoo	10,460	0.5	0.01	0.0082
Hair conditioner	3,920	0.5	0.01	0.0031
Shower gel	18,670	0.5	0.01	0.0146
Hand wash soap	20,000	0.5	0.01	0.0156
Hair styling products	4,000	0.5	0.1	0.0313
Total				**1.6758**

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	0.5	20	1	20	50	1	10	**0.0161**

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	0.5	0.95	10	0.0171
Fabric softener	90	0.5	0.95	10	0.0067
Total					**0.0238**

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	0.5	1,980	0.01	0.01	0.007	0.0002
Dishwashing liquid	3	0.5	1,980	0.009	0.01	0.03	0.0013
All-purpose cleaner	1	0.5	1,980	1	0.01	0.007	0.0108

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)
Total							**0.0122**

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 1.7279 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 conservative hair spray inhalation exposure assessment parameters, (in particular assuming an airspace volume of 1 m^3 in zone 1), and the aggregate exposure form the 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 exposure factors (e.g. air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. Due to the manufacture process not all of the possible isomers covered by the generic name of the notified chemical were present in the test substance, which was used in the toxicological studies.

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 > 4.53 mg/L/4 hour; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 750 mg/kg/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic
Genotoxicity – *in vivo* micronucleus 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 (178.27 g/mol), water solubility (0.0486 – 0.166 g/L) and partition coefficient (log Pow = 3.48-3.53 at 22.8 °C) of the notified chemical, absorption across biological membranes may occur.

Acute toxicity

The notified chemical was of low acute oral, dermal and inhalation toxicity when tested in rats.

Irritation

Based on the data in studies conducted in rabbits, the notified chemical is expected to be non-irritating to the skin and slightly irritating to eyes.

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 100% concentration).

Repeated dose toxicity

A repeated dose oral (gavage) toxicity study was conducted in rats, in which the notified chemical was administered at 30, 300 and 1000/750 mg/kg bw/day for 28 consecutive days. The dose of 1000 mg/kg/day was associated with severe clinical signs resulting in the premature termination of 1 female animal and necessitating the reduction of the high dosage to 750 mg/kg/day from Day 2.

There were some statistically significant changes in organ weights of the animals treated at 300 mg/kg bw/day or 1000/750 mg/kg bw/day. However, no histopathological changes were noted in these organs.

The No Observed Adverse Effect Level (NOAEL) was established as 750 mg/kg bw/by the study authors.

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

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available information the notified chemical is expected to be of low toxicity, although mild irritation to the eyes may occur.

Reformulation
During reformulation workers may be at risk of mild eye irritation when handling the notified chemical at up to 100% concentration. It is anticipated by the notifier that engineering controls such as enclosed and automated processes and sufficient ventilation will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit workers exposure.

Under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners, hair and beauty care professionals will handle the notified chemical in a variety of cosmetic and household products (at various concentrations). Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health
Members of the public may be repeatedly exposed to the notified chemical during the use of a variety of cosmetic and household products at various 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 of 1.7279 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 750 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 434. 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 ≤ 3% in leave-on/rinse-off cosmetics, ≤ 5% in fine fragrances, ≤ 3% in household cleaning products, ≤ 5% in instant action air fresheners and ≤ 10% in other types of air fresheners.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical in a variety of cosmetic and household products at various concentrations assessed is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as a component of end-use cosmetic and household products, or imported in the pure form or as a component of fragrance solutions for reformulation into the end-use products. In general, the reformulation processes are expected to involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into end-use containers. Liquid waste from cleaning of the reformulation equipment will either be reused or disposed of through an approved waste management facility. Release of the notified chemical to the environment in the event of accidental spills or leaks during reformulation, storage and transport is expected to be absorbed on suitable materials and disposed of to landfill in accordance with local government regulations. Empty containers containing the notified chemical will be rinsed and then either be recycled or disposed of through an approved waste management facility.

RELEASE OF CHEMICAL FROM USE

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

RELEASE OF CHEMICAL FROM DISPOSAL

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

7.1.2. Environmental Fate

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

Ready biodegradation tests conducted on the notified chemical indicates that it is readily or at least inherently biodegradable (84% degradation over 28 days in OECD 301 C test, and 71% degradation over 28 days in OECD 301 F test). For details of the biodegradation studies, please refer to Appendix C. The notified chemical is expected to sorb to sludge at STPs based on its hydrophobic structure. Therefore, the notified chemical is expected to be removed effectively through biodegradation and adsorption to sludge at STPs, and only a small portion of the notified chemical may be released to surface waters. A proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation, or disposed of to landfill. The notified chemical residues in landfill and soils are expected to have low mobility based on its surface activity and soil adsorption coefficient log K_{oc} = 2.4 – 2.5. The notified chemical is not expected to bioaccumulate based on its biodegradability and surface activity. In the aquatic and soil compartments, the notified chemical is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The half-life of the notified chemical in air is calculated to be 0.5 h, based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA, 2012). Therefore, the notified chemical is not expected to persist in the air compartment.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume the worst case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. It is also assumed under the worst-case scenario that there is no removal of the notified chemical during sewage treatment processes. The resultant PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year

Days per year where release occurs	365	days/year
Daily chemical release:	2.7	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.7 µg/kg.

7.2. Environmental Effects Assessment

The results from the ecotoxicological investigation conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C. Due to the manufacture process not all of the possible isomers covered by the generic name of the notified chemical were present in the test substance, which was used in the toxicological studies.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h EC50 = 23.1 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 22.8 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 = 28.5 mg/L	Harmful to alga
Inhibition of Bacterial Respiration	3 h IC50 = 189 mg/L	Does not inhibit microbial activity in STPs

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS), the notified chemical is expected to be harmful to aquatic organisms. Therefore, the notified chemical is formally classified as "Acute Category 3; Harmful to aquatic life" under the GHS (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated based on the most sensitive endpoint for Daphnia as shown in the table below. An assessment factor of 100 was used given the acute endpoint for three trophic levels is available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Daphnia 48 h EC50	22.8	mg/L
Assessment Factor	100	
Mitigation Factor	1	
PNEC:	228	µg/L

7.3. Environmental Risk Assessment

Based on the above predicted PEC and PNEC, the following Risk Quotient (Q = PEC/PNEC) has been calculated.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	228	**0.002**
Q - Ocean	0.06	228	**0.000**

The conservative risk quotient for discharge of effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. Based on its biodegradability and surface activity, the notified chemical is not expected to be bioaccumulative. Therefore, on the basis of the predicted PEC/PNEC ratio, the maximum annual importation volume, and the assessed use pattern as a component of cosmetic and household products, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -11 °C (melting point) at 101.3 kPa
-30 – -33 °C (freezing point) at 101.3 kPa

Method OECD TG 102 Melting Point/Melting Range
Remarks Determined by differential scanning calorimetry
Test Facility Consilab (2014a)

Boiling Point 250 -255 °C at 101.3 kPa

Method OECD TG 103 Boiling Point
Remarks Determined by differential scanning calorimetry
Test Facility Consilab (2014a)

Density 973.5 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids
Remarks Pycnometer method
Test Facility Dr U Noack-Laboratorien (2014a)

Vapour Pressure 1.26×10^{-3} kPa at 20 °C
2.12×10^{-3} kPa at 25 °C
2.25×10^{-2} kPa at 50 °C

Method OECD TG 104 Vapour Pressure
Remarks Determined by differential scanning calorimetry (thermal stability) and effusion method
Test Facility Consilab (2014b)

Water Solubility 0.0486 – 0.166 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 (2014b)

Hydrolysis as a Function of pH

Method Not stated, the procedure is similar to OECD TG 111 Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ (year)*
2	40	>1
5	40	>1
7	40	>1
8.5	40	>1
12	40	>1

Remarks The notified chemical is considered hydrolytically stable
Test Facility Firmenich S.A Geneva (2016)

Partition Coefficient (n-octanol/water) log Pow = 3.48 - 3.53 at 23 °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 (2015a)

Surface Tension 53.59 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions
Remarks	Concentration: 90% of the saturation level
Test Facility	Dr U Noack-Laboratorien (2014c)

Adsorption/Desorption log K_{oc} = 2.4 - 2.5 at 23.6 °C

Method	OECD TG 121 Adsorption - Desorption Using HPLC Method EC Council Regulation No 440/2008 C.19 Adsorption - Desorption
Remarks	HPLC Method
Test Facility	Dr U Noack-Laboratorien (2015b)

Flash Point 119.5 °C at 101.1 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Closed cup method
Test Facility	Consilab (2014c)

Autoignition Temperature 260 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Test Facility	Consilab (2014d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Sprague Dawley Crl:CD (SD)
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations. A preliminary study (Group 1) was conducted in 3 female animals at a dose of 2,000 mg/kg bw. The dose of 2,000 mg/kg bw was selected for Group 2 study based on the results (no mortalities) of the Group 1 study.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	One animal was killed due to poor clinical condition on Day 2. Prior to death, unsteady gait, tremors, uncoordinated gait, piloerection, hunched posture, flat posture, shallow breathing and reduced body temperature were noted. These signs were noted from approximately 30 minutes after dosing. Unsteady gait, tremors, uncoordinated gait and piloerection, loose faeces, hunched posture, reduced activity, shallow breathing, elevated gait and urine staining were noted in the remaining animals. These signs were first noted approximately 30 minutes after dosing and recovery was complete by Day 4 or 6.
Effects in Organs	Pallor (pale colour) of the lungs, liver and kidneys and yellow fluid content in the small and large intestines were noted in the killed animal and pallor of the kidneys was noted in one of the remaining animals at macroscopic examinations.
Remarks - Results	Slightly low body weight gain was noted during the second week for two surviving animals in the Group 2. All other animals achieved satisfactory body weight gains throughout the study.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	HLS (2014)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity
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 animals 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	Very slight erythema was noted at the test sites of 4 female animals 1 day after dosing. No signs of dermal irritation were noted at the test sites of all male animals and the remaining female animal.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	Gains in body weight were considered by the study authors to be within the historical range for this strain.

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

TEST FACILITY Harlan (2014a)

B.3. Acute toxicity – inhalation

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	2.68 μm (mean MMAD) with a geometric standard deviation of 2.1 μm
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration g/m³*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	35.1	4.53	1/10

LC50	> 4.53 mg/L/4 hours
Signs of Toxicity	During exposure, 1 female animal showed decreased respiratory rate. On removal from the chamber, all animals showed decreased respiratory rate and ataxia. All female animals also showed body tremors and increased activity. Nine animals (5 males and 4 females) showed increased respiratory rate, hunched posture and pilo-erection 1 day post-exposure and appeared normal from Days 7 to 8 post-exposure. One female animal showed decreased respiratory rate, ataxia, dehydration, lethargy, ptosis and splayed gait 1 day post-exposure and was euthanised.
Effects in Organs	Abnormally red lungs with dark patches were noted in 1 male animal and pale liver and kidneys were noted in 1 female animal. No macroscopic abnormalities were noted in 7 surviving animals at necropsy. Dark liver and kidneys were noted at necropsy in the female animal that was euthanised. The death was subsequently considered by the study authors to be mainly attributable to systemic toxicity.
Remarks - Results	All animals showed body weight losses on Day 1 post-exposure. Body weight gains were noted in all surviving animals during the remainder of the recovery period.

CONCLUSION The notified chemical is of low acute toxicity via inhalation.

TEST FACILITY Harlan (2014b)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 3F
Vehicle None
Observation Period 72 hours
Type of Dressing Semi-occlusive
Remarks - Method No significant protocol deviations

RESULTS
Remarks - Results No irritation reactions were noted immediately after patch removal and at the 1-hour, 24-hour, 48-hour and 72-hour observations.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Harlan (2014c)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 3F
Vehicle None
Observation Period 14 days
Remarks - Method No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	2	1	1	2	< 14 days	0
Conjunctiva: chemosis	1.7	0.3	1	2	< 14 days	0
Conjunctiva: discharge	1	0	0	2	< 7 days	0
Corneal opacity	0	0	0.3	1	< 48 hours	0
Iridial inflammation	1	0	0.7	1	< 7 days	0

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

Remarks - Results A single application of the test substance produced conjunctival irritation (maximum value of 2), iridial inflammation (maximum value of 1) and diffuse corneal opacity (maximum value of 1). Two treated eyes appeared normal at the 72-hour observation and 1 treated eye appeared normal at the 14-day observation.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Harlan (2015a)

B.6. Skin sensitisation

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: 20% topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 10 F Control Group: 5 F
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: 20% topical: 100%
Signs of Irritation	In the negative control group, no irritation reactions were noted after the 1st induction (intradermal) and dryness was noted in 1/5 animals after 2nd induction (topical). In the treated group, no irritation reactions were noted after the 1st induction (intradermal) and dryness was noted in 10/10 animals after 2nd induction (topical).
CHALLENGE PHASE	
1st challenge	Topical: 100%
Remarks - Method	

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*	
		24 h	*48 h*
Test Group	100%	0/5	0/5
Control Group (vehicle)	100%	1/10	0/10

Remarks - Results	No mortalities were noted. The mean body weight and body weight gain were not affected. No skin reactions were noted after the challenge in the vehicle control group. Discrete erythema was noted in 1/10 treated animal at the 24-hour reading. No irritation reactions were noted in treated animals at the 48-hour reading.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.
TEST FACILITY	Phycher (2015)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week

	Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	30	0/10
mid dose	5 per sex	300	0/10
high dose	5 per sex	1000/750*	1/10
control recovery	5 per sex	0	0/10
high dose recovery	5 per sex	1000/750*	0/10

* The dose was reduced to 750 mg/kg bw from 1000 mg/kg bw after 1 day.

Mortality and Time to Death

One female treated at 1000 mg/kg bw/day was killed on Day 1 due to clinical signs including piloerection, partially closed eyelids, impaired locomotion, splayed hind limbs, elevated and swaying gait, decreased activity, uncoordinated behaviour and body tremors. No pathological causes for these signs were established at terminal examinations.

Clinical Observations

Swaying and elevated gait, body tremors, uncoordinated behaviour, piloerection and abnormally cold to touch were noted in animals treated at 1000 mg/kg/day on Day 1. All animals had recovered by the morning on Day 2. Due to the severity of the signs and poor prognosis for surviving the 28 days treatment period, the high dose was reduced to 750 mg/kg bw/day from Day 2. Following the dose reduction, elevated gait, piloerection, eating of bedding, decreased activity, and partially closed eyelids were noted for a small number of animals on Days 2 and/or 3.

Chin rubbing was noted for 2 female animals treated at 300 mg/kg/day and was considered by the study authors to be typically related to the taste of the test substance and not of toxicological importance.

No treatment-related signs were noted after Day 5 of treatment.

Sensory reactivity responses and grip strength were unaffected by treatment.

Motor activity in females was considered by the study authors to be unaffected by treatment. During Week 4 of treatment motor activity for males treated at 1000/750 mg/kg/day showed a statistically significant increase compared to the control group. During Week 2 of recovery, the same pattern occurred with high and low beam scores for male animals previously treated at 750/1000 mg/kg/day being statistically significantly higher than controls and with the 2 animals that had shown the highest activity after 28 days of treatment similarly showing the highest activity during Week 2 of recovery. These changes were considered by the study authors to be of doubtful toxicological significance.

Overall body weight gain for male animals treated at 1000/750 mg/kg/day was lower than that of the controls, but recovery was evident following cessation of treatment.

Food and water consumption were high during the treatment period for both sexes treated at 1000/750 mg/kg/day but not during the recovery period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology

There were statistically significant increases in group mean prothrombin and activated partial thromboplastin times for male animals treated at 300 or 1000/750 mg/kg/day. These changes had resolved following recovery.

Clinical Biochemistry

Statistically significant increases in urea and blood urea nitrogen concentrations were noted for male animals

treated at 300 or 1000/750 mg/kg/day. Low glucose concentration (statistically significant) was noted for female animals treated at 1000/750 mg/kg/day or 300 mg/kg/day. Statistically significant increases in cholesterol, triglyceride and bile acid concentrations were noted for female animals treated at 1000/750 mg/kg/day. Statistically significant decreases in sodium and chloride concentrations were noted for female animals treated at 1000/750 mg/kg/day and in albumin concentration for male animals treated at 300 or 1000/750 mg/kg/day with an associated low albumin/globulin ratio for male animals at the 1000/750 mg/kg/day dose. All changes had fully or partially resolved following recovery.

Urinalysis
A statistically significant decrease in pH, total protein and total potassium was noted for male animals treated at 1000/750 mg/kg/day. A statistically significant increase in total protein, chloride and creatinine output was noted for female animals treated at 1000/750 mg/kg/day and a statistically significant increase in specific gravity was noted for male animals treated at 750/1000 mg/kg/day. None of these changes were apparent following recovery.

Effects in Organs
When compared with the controls, statistically significantly higher body weight-adjusted liver weights were noted for animals treated at 300 or 1000/750 mg/kg/day. Body weight-adjusted kidney weights were statistically significantly higher for male animals treated at 300 or 1000/750 mg/kg/day and body weight-adjusted ovary weights were low for female animals treated at 1000/750 mg/kg/day. After the 14 day recovery period male animals in the 1000/750 mg/kg/day dose group had statistically significantly higher body weight-adjusted epididymides, while female animals in the 1000/750 mg/kg/day dose group had lower thymus weights and higher terminal body weights.

No test substance-related lesions were noted at macroscopic and microscopic examinations.

Remarks – Results
The study authors stated that the dose of 1000 mg/kg/day was associated with severe clinical signs resulting in the premature termination of 1 female animal and necessitating the reduction of the high dosage to 750 mg/kg/day from Day 2. At 750 mg/kg/day, there were transient clinical signs, increased motor activity and treatment-related effects on body weight, water consumption, clotting factors, clinical chemistry and urine parameters and liver and kidney weights. These findings showed at least partial recovery following recovery and no pathological changes were noted. None of the findings were considered by the study authors to be adverse at the severity noted in this study.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 750 mg/kg bw/ by the study authors.

TEST FACILITY	HLS (2015)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	With metabolic activation: 0.15-500 µg/plate (TA98, TA1537, WP2uvrA) and 0.15-150 µg/plate (TA1535, TA100) Without metabolic activation: 0.15-500 µg/plate (TA100, WP2uvrA) and 0.15-150 µg/plate (TA1535, TA1537, TA98)
Vehicle	Dimethyl sulphoxide
Remarks - Method	A dose range-finding study was carried out at 1.5–5,000 µg/mL to select the concentration 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	≥ 150	≥ 150	> 5000	negative
Present				
Test 1	≥ 150	≥ 150	> 5000	negative

Remarks - Results

No toxicologically 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, with one exception. A statistically significant increase in the frequency of revertant colonies was observed in the absence of metabolic activation with TA1537 at 50 μg/plate. There was no dose response relationship or reproducibility and it was within the range of the historical controls and subsequently the studiy authors considered the finding to be of no biological relevance.

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

CONCLUSION

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

TEST FACILITY

Harlan (2014d)

B.9. Genotoxicity – *in vitro*

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 observed in the range-finding study carried out at 7 – 1780 μg/mL.

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

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 60*, 90*, 180*, 240, 300, 360	4 h	24 h
Test 2	0*, 15, 30, 45*, 60*, 90*, 120	24 h	24 h
Present			
Test 1	0*, 60*, 90*, 180*, 240*, 360, 450	4 h	24 h
Test 2	0*, 60*, 90*, 180*, 240, 300, 360	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	≥ 445	> 180	≥ 445	negative
Test 2	> 111.25	≥ 90	≥ 445	negative
Present				
Test 1	≥ 445	> 240	≥ 890	negative
Test 2		> 180		negative

* Based on mitotic index ≤ 50%.
\# Noted in the Preliminary Test

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 (2015b)

B.10. Genotoxicity – *in vitro*

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 487 *In vitro* Mammalian Cell Micronucleus 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 observed in the range-finding study carried out at 6.96 – 1783 µg/mL.

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

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 60, 90, 120*, 150*, 180*, 210, 240, 300	4 h	32 h
Test 2	0*, 27.75*, 55.5*, 111*, 148, 185, 222	24 h	52 h
Present			
Test 1	0*, 60, 90, 120, 150, 180*, 210*, 240*, 300	4 h	32 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	≥ 445.75	≥ 210	≥ 891.5	negative
Test 2	≥ 222.88	≥ 111	≥ 445.75	negative
Present				
Test 1	≥ 445.75	≥ 300	≥ 445.75	negative

* Based on cytokinesis-block proliferation index ≤ 50%
\# Noted in the Preliminary Test

Remarks - Results

In both main tests, no statistically significant increases in the frequency of binucleate cells with micronuclei 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 (2015c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability study 1

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Oxygen Consumption Analyser and Gas Chromatography (GC)
Remarks - Method	No significant deviations from the test guidelines were reported. The test substance was directly added into culture bottles before mineral mediums were added. A toxicity control was run.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation calculated from BOD*	*Day*	*% Degradation calculated from BOD*
7	4	7	70
14	49	14	74
21	71	21	75
28	84	28	75

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, aniline surpassed the threshold level of 60 % within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical calculated from BOD after 28 days was 84%. The degree of degradation of the notified chemical calculated from direct GC measurement of 3 isomers after 28 days was 100% for all isomers.
CONCLUSION	The notified chemical is readily degradable.
TEST FACILITY	Institute of Ecotoxicology Co., Ltd. (2014)

C.1.2. Ready biodegradability study 2

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Oxygen Consumption Analyser
Remarks - Method	No significant deviations from the test guidelines were reported. The test substance was directly added into culture bottles before mineral mediums were added.

Results

Test substance		*Sodium benzoate*	
Day	*% Degradation calculated from BOD*	*Day*	*% Degradation calculated from BOD*
7	14	7	78
14	54	14	86
21	64	21	89
28	71	28	89

Remarks - Results: All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 60 % within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The 10 day window ended up on day 16 to day 17 of the test with degree of degradation of 57% to 59%. The degree of degradation of the notified chemical after 28 days was 71%.

CONCLUSION: The notified chemical is not readily degradable, but shows inherently biodegradability.

TEST FACILITY: Guangdong Detection Center of Microbiology (2015a)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test – Static
OECD Series on Testing and Assessment number 23, Guidance Document on Aquatic Toxicity Testing of Difficult Substance and Mixtures
The Guidelines for the Testing of Chemicals, Effects on Biotic Systems, 203 Fish Acute Toxicity Test, China Environmental Press
GB/T 27861-2011, Chemicals Fish Acute Toxicity Test, China Standard Press

Species: *Danio rerio*
Exposure Period: 96 hours
Auxiliary Solvent: None
Water Hardness: 118 mg $CaCO_3$/L
Analytical Monitoring: Gas Chromatography (GC)
Remarks – Method: No significant deviations from the test guidelines were reported. The stock solution of 100 mg/L was freshly prepared with dilution water and stirred for 1 hour. Further test concentrations were prepared by diluting the 100 mg/L stock solution.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	< LOD*	10	0	0	0	0	0
6.79	6.53	10	0	0	0	0	0
9.84	9.58	10	0	0	0	0	0
14.3	13.6	10	0	0	0	0	0
20,7	20.4	10	0	20	20	20	20
30.0	30.6	10	100	100	100	100	100

*Limit of detection (LOD) = 0.113 mg/L

LC50: 23.1 (95% CL of 21.1-25.4) mg/L at 96 hours (calculated by Trimmed

	Spearman-Karber software v1.5 from US EPA)
Remarks – Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified chemical is harmful to fish.
TEST FACILITY	Guangdong Detection Center of Microbiology (2015b)

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	None
Water Hardness	263 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography – Mass Spectrometry (GC-MS)
Remarks - Method	No significant deviations from the test guidelines were reported. The stock solution of 100 mg/L was freshly prepared with dilution water and stirred for 1 hour. Further test concentrations were prepared by diluting the 100 mg/L stock solution. The test solution was changed daily. Measured concentrations of the test substrate at 24 hours and 48 hours were in the range of 91 to 109% of nominal values.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	<LOQ**	5	0	0
6.25	5.98	5	0	0
12.5	12.4	5	0	5
25.0	23.1	5	45	60
50.0	48.2	5	85	90
100	98.7	5	100	100

**Limit of Quantitation (LOQ) = 5 µg/L

LC50	22.8 (95% CL of 19.7-25.4) mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified chemical is harmful to aquatic invertebrates.
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
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.00, 3.16, 10.0, 31.6, 100 mg/L Actual: 0.92, 3.05, 10.1, 31.2, 95.7 mg/L
Auxiliary Solvent	None
Water Hardness	Not determined
Analytical Monitoring	Gas Chromatography – Mass Spectrometry (GC-MS)

Remarks - Method	No significant deviations from the test guidelines were reported. The stock solution of 100 mg/L was freshly prepared with dilution water and stirred for 1 hour. Further test concentrations were prepared by diluting the 100 mg/L stock solution.

RESULTS

Biomass		*Growth*	
EC50 *mg/L at 72 h*	*NOEC* *mg/L*	*EC50* *mg/L at 72 h*	*NOEC* *mg/L*
28.5 (95% CI 27.1-29.9)	3.16	12.9 (95% CI 10.6-16.1)	3.16

Remarks - Results	All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is harmful to alga.

TEST FACILITY Dr U Noack-Laboratorien (2015d)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test
Inoculum	Activated sludge from a local STP
Exposure Period	3 hours
Concentration Range	Nominal: 10, 32, 100, 320, 1,000 mg/L
Remarks – Method	No significant deviations from the test guidelines were reported. The test substance was pipetted directly in Erlenmeyer flasks before starting the test. The test concentration of 1,000 mg/L is above the test substance's water solubility.

RESULTS

IC50	189 (95%CI of 177-303) mg/L
Remarks – Results	All validity criteria for the test were satisfied.

CONCLUSION Not inhibit microbial activity at STPs

TEST FACILITY Dr U Noack-Laboratorien (2014d)

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