File No.: STD/1707

February 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexanecarboxylic acid, 4-methyl-2-oxo-, ethyl ester

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1707	International Flavours and Fragrances (Australia) Pty Ltd	Cyclohexanecarboxylic acid, 4-methyl-2-oxo-, ethyl ester	Yes	≤ 5 tonnes per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information, the notified chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The hazard classification applicable to the notified chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Skin Sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

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

Hazard Classification	*Hazard Statement*
Chronic (Category 3)	H412 – Harmful to aquatic life 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:
  – Skin Sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Impervious gloves
  - Protective clothing
  - Respiratory protection if aerosols or mists are expected to be generated

  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.

Emergency procedures

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

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical n 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.

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 final use concentration of the notified chemical exceeds 0.9% in deodorants, 2% in leave-on cosmetics, 1% in fine fragrances, 17% in leave-on hair products or 30% in rinse-off cosmetics and household products;

or

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

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

Safety Data Sheet
The SDS of the notified chemical and a product containing the notified chemical provided by the notifier were 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
Standard: Chemical other than polymer (more than 1 tonne per year)

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are varied for hydrolysis as a function of pH and dissociation constant.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China, EU and Philippines

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Toffeetone

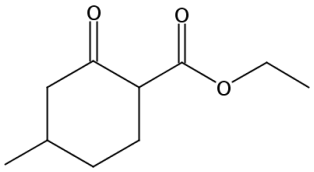
CAS NUMBER
13537-82-1

CHEMICAL NAME
Cyclohexanecarboxylic acid, 4-methyl-2-oxo-, ethyl ester

OTHER NAME(S)
4-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester
FRET 13-0545 (code in study reports)

MOLECULAR FORMULA
$C_{10}H_{16}O_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
184.23 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
93.2%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	Cyclohexanone, 3-methyl-		
CAS No.	591-24-2	*Weight %*	~ 2.8
*Hazardous Properties**	H226 - Flammable liquid and vapour H302 – Harmful if swallowed H312 – Harmful in contact with skin H315 – Causes skin irritation H319 – Causes serious eye irritation H332 – Harmful if inhaled H335 – May cause respiratory irritation H336 – May cause drowsiness or dizziness		

* From ECHA C&L Inventory

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name	Cyclohexanecarboxylic acid, 2-methyl-6-oxo-, ethyl ester		
CAS No.	58019-68-4	*Weight %*	~ 4

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid

Property	***Value***	***Data Source/Justification***
Melting Point/Freezing Point	< -80 °C	Measured
Boiling Point	244.6 °C at 98.9 kPa	Measured
Density	1,040 kg/m^3 at 20 °C	Measured
Vapour Pressure	2.8 × 10^{-2} kPa at 25 °C	Measured
Water Solubility	2.56 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Expected to slowly hydrolyse in the environment pH of 4-9
Partition Coefficient (n-octanol/water)	log Pow = 4.36 at 30 °C	Measured
Adsorption/Desorption	log K_{oc} = 3.16 at 30 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Surface Tension	69.1 mN/m at 20 °C	Measured
Flash Point	106 °C at 100.7 kPa	Measured
Flammability	Not determined	Not expected to be highly flammable based on the measure flash point
Autoignition Temperature	230 °C at 102.2 – 102.38 kPa	Measured
Explosive Properties	Predicted negative	Based on the chemical structure
Oxidising Properties	Predicted negative	Based on the chemical structure

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

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

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

The notified chemical has a flash point of 106 ºC which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the notified chemical may be considered as a Class C2 combustible liquid if the chemical has a flash point below the boiling point.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported into Australia as a component of fragrance oil formulations at ≤ 10% concentration.

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

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

PORT OF ENTRY
Melbourne

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

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of fragrance oil formulations in 208 L polypropylene lined steel drums. Within Australia the drums will be transported mainly by road to the warehouse for storage and later distributed to the formulators by road for reformulation. Finished consumer products containing the notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products. The proposed maximum use concentration of the notified chemical in various consumer products will be:

Finished consumer product	***Maximum proposed use concentration (%)***
Body lotion, face cream and hand cream	1
Fine fragrance	1
Deodorant	0.5
Other cosmetic (such as hair spray, hair styling products, makeup remover)	2
Rinse-off personal care such as shampoo, shower gel, hand wash soap and facial cleanser)	5
Household products	5

OPERATION DESCRIPTION

Reformulation
Reformulation of fragrance oil formulations containing the notified chemical at ≤ 10% concentration into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end-use products into containers of various sizes.

End-use
End-use products containing the notified chemical at ≤ 5% concentration will be used by consumers and professionals such as hairdressers, beauticians or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	Incidental	250
Mixing and compounding	4	250
Drum handlers	1	250
Drum cleaners	2	250
Equipment cleaners	2	250
Quality control	1	250
Professional end users	8	250

EXPOSURE DETAILS

Transport and storage
Transport, storage and warehouse workers may come into contact with the notified chemical as a component of fragrance formulations at ≤ 10% concentration, only in the unlikely event of accidental rupture of containers.

Reformulation
During reformulation, dermal and ocular exposure of workers to the notified chemical at ≤ 10% concentration may occur during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. Due to the notified chemical's low vapour pressure (2.8×10^{-2} kPa at 25 °C), inhalation exposure is not expected, unless aerosols or mists are formed.

The notifier stated that exposure is expected to be minimised through the use of local exhaust ventilation and/or enclosed systems, and through the use of personal protective equipment (PPE) such as protective clothing, goggles, impervious gloves and respiratory protection (in cases where there is inadequate ventilation).

End-use
Exposure to the notified chemical in end-use products at ≤ 5% concentration may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hair dressers and workers in beauty salons), or the use of household cleaning products in the cleaning industry. The principal route of exposure will be dermal, while ocular exposure and inhalation exposure are also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the products containing the notified chemical.

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

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

Endpoint	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity
Acute dermal toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity
Acute inhalation toxicity – rat	LC50 > 5 mg/L/4 hour; low toxicity
Skin corrosion – *in vitro* EpiDerm model	non-corrosive
Skin irritation – *in vitro* EpiSkin model	non-irritating
Eye irritation – *in vitro* bovine corneal opacity and permeability (BCOP) test	non-irritating
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3 = 82%)

Endpoint	*Result and Assessment Conclusion*
Skin Sensitisation – human repeated insult patch test (HRIPT) (10%)	no evidence of sensitisation
Repeat dose oral toxicity – rat, 28 days	NOAEL = 12,500 ppm (917/869 mg/kg bw/day (m/f))
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosomal aberration test in human lymphocytes	non genotoxic

Toxicokinetics
No information on the toxicokinetics of the notified chemical was provided. For dermal absorption, molecular weights less than 100 g/mol favour dermal uptake and molecular weights above 500 g/mol do not favour absorption (ECHA, 2017). Substances with water solubility between 0.1-10 g/L and partition coefficients (log Pow) between 1 – 4 are likely to have moderate to high dermal absorption, although with log Pow values above 4 the rate of penetration through the skin may be limited by the rate of transfer between the stratum corneum and the epidermis (ECHA, 2017). Based on the low molecular weight (< 500 g/mol), water solubility (2.56 g/L at 20 °C) and partition coefficient (log Pow = 4.36) of the notified chemical, there is potential for the chemical to cross biological membranes.

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

Irritation
In two *in vitro* skin corrosion and skin irritation studies, the notified chemical was found to be non-corrosive and non-irritating.

In an *in vitro* eye irritation test, the notified chemical was determined to not require classification for eye irritation.

Sensitisation
The notified chemical was found to be a weak skin sensitiser in a mouse Local Lymph Node Assay (LLNA) with stimulation indices of 1.18, 1.66 and 3.75 at 25, 50 and 100% concentrations, respectively. The EC3 value was calculated to be 82%.

The notified chemical (at 10% concentration) was found to be negative in a human repeated insult patch test.

Repeated Dose Toxicity
A repeated dose oral (diet) toxicity study on the notified chemical was conducted in rats, in which the notified chemical was administered at 1,400, 4,200 and 12,500 ppm (equivalent to 96/94, 307/280 and 917/869 mg/kg bw/day in males/females) for 28 consecutive days, with a 14-day recovery period at the high dose. The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 12,500 ppm.

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

Health Hazard Classification
Based on the available information, the notified chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The hazard classification applicable to the notified chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation
Based on the toxicological information provided, the notified chemical is a weak skin sensitiser.

6.3.1. Occupational Health and Safety

Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical at ≤ 10% concentration during reformulation. Given the notified chemical is a skin sensitiser caution should be exercised

when handling the notified chemical during reformulation processes. The use of local ventilation, enclosed/automated processes and PPE (i.e. protective clothing, goggles, impervious gloves and respiratory protection, if inhalation exposure may occur) are expected to minimise the potential for exposure.

Therefore, provided control measures are in place to minimise worker exposure, 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. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the notified chemical is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2 below.

6.3.2. Public Health

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

Sensitisation
Based on the results of an LLNA study, the notified chemical is considered to be a weak skin sensitiser (EC3 = 82%). Methods for the quantitative risk assessment for dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). As shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in various cosmetic product categories was estimated using the worst case example in each of the categories (SCCS, 2012 Cadby *et al.*, 2002). Consideration of available information and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 71.07 µg/cm^2/day to be estimated for the notified chemical. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300. The maximum allowable concentration for different cosmetic product categories was also calculated so the values (rounded down) can be used to restrict the concentration of the notified chemical in each category based on the potential risk of sensitisation.

Product type	***Proposed maximum use concentration (%)***	***CEL (µg/cm^2)***	***AEL (µg/cm^2)***	***Allowable concentration***
Deodorant	0.5	37.5	71.07	0.95
Leave-on cosmetics (assumed: face cream)	1		71.07	2.61
Fine fragrances	1	37.5	71.07	1.90
Leave-on hair products (assumed: hair styling products)	2	7.92	71.07	17.94
Rinse-off cosmetics (assumed: hand wash soap)	5	11.63	71.07	30.56

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at the proposed concentrations of ≤ 0.5% in deodorants, ≤ 1% concentration in leave-on cosmetics, ≤ 1% in fine fragrances, ≤ 2% in leave-on hair products and at ≤ 5% in rinse-off cosmetic products (using hand wash soap as a worst case example), is not considered to be unreasonable. Additionally, the use of the notified chemical at concentrations of ≤ 0.9% in deodorants, ≤ 2% in leave-on cosmetics, ≤ 1% in fine fragrances, ≤ 17% in leave-on hair products and ≤ 30% in rinse-off cosmetics was also calculated as not considered to be unreasonable.

Based on the expected low exposure from household products, 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.

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 as a component of finished fragrance oil for reformulation into cosmetic and household products. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

The fragrance formulations containing the notified chemical will be blended with other ingredients in the manufacture of cosmetic and household products within a fully enclosed environment. Wastes containing the notified chemical generated during reformulation include equipment wash water, empty import containers and spilt materials. Empty import containers wash waters are expected to be recycled into subsequent blending processes or released to sewers, or disposed of to landfill in accordance with local government regulations. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic formulations and household products across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that approximately 1% of the product containing the notified chemical will remain in end-use containers. Wastes and residue of the notified chemical in empty containers is 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 Australia, the majority of the notified chemical is expected to be released to sewers on a nationwide basis. The notified chemical is readily biodegradable (82.1% in 28 days). For the details of the environmental fate studies, please refer to Appendix C.

The half-life of the notified chemical in air is calculated to be 0.99 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA 2011). Therefore, if released to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

A significant proportion of the notified chemical may not remain in the aqueous phase in the sewage treatment plants (STPs) based on its water solubility, medium partition and adsorption coefficients and ready biodegradability. A proportion of the notified chemicals may be applied to land when effluent is used for irrigation or disposed of to landfill as waste. The notified chemical residues in landfill and soils are expected to have moderate mobility based on its soil adsorption coefficient (log Koc = 3.16). The notified chemical has potential to bioaccumulate (log P_{OW} = 4.36); however, this is not expected due to its ready biodegradability. In surface waters, soils and landfill, the notified chemical is expected to eventually degrade through both biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the notified chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. The extent to which the notified chemical is removed from the effluent in STP processes based on the properties of the notified chemical has not been considered for this scenario, and therefore no removal of the notified chemical during sewage treatment processes, is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows.

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Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	5,000	kg/year

Days per year where release occurs	365	days/year
Daily chemical release:	13.70	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	2.81	µg/L
PEC - Ocean:	0.28	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 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 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 2.81 µg/L may potentially result in a soil concentration of approximately 0.018 mg/kg.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 46 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 61 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h ErC50 = 55 mg/L NOEC = 6.8 mg/L	Harmful to algae

Based on the ecotoxicological endpoints for the notified chemical, it is expected to be harmful to fish, aquatic invertebrates 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 3; Harmful to aquatic life". Based on the acute data and potential to bioaccumulate, the notified chemical is classified as "Chronic Category 3; Harmful to aquatic life with long lasting effect".

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive acute endpoint for fish and assessment factor of 100 given three acute endpoints for three trophic levels and one chronic endpoint are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish).	46	mg/L
Assessment Factor	100.00	
Mitigation Factor	1.00	
PNEC:	460	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	2.81	460	0.006
Q - Ocean:	0.281	460	< 0.0001

The Risk Quotients (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemical has been calculated to be < 1 for both river and ocean compartments indicating that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The notified chemical is not expected to bioaccumulate. On the basis of the PEC/PNEC ratio and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -80 °C

Method	OECD TG 102 Melting Point/Melting Range
Remarks	Determined using differential scanning calorimetry
Test Facility	CRL (2017a)

Boiling Point 244.6 °C at 98.9 kPa

Method	OECD TG 103 Boiling Point
Remarks	Determined using differential scanning calorimetry
Test Facility	CRL (2017a)

Density 1,040 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Determined using a Pycnometer
Test Facility	CRL (2017a)

Vapour Pressure 2.8×10^{-2} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure
Remarks	Determined using a vapour pressure balance
Test Facility	Envigo (2017a)

Water Solubility 2.56 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	Envigo (2017b)

Partition Coefficient (n-octanol/water) log Pow = 4.36 at 30 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method/Flask Method. Other entities with lower log Pow values were identified but were considered to be impurities.
Test Facility	Envigo (2017b)

Adsorption/Desorption log K_{oc} = 3.16 at 30 °C

Method	OECD TG 106 Adsorption – Desorption Using a Batch Equilibrium Method
Remarks	HPLC method
Test Facility	Envigo (2018)

Surface Tension 69.1 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions
Remarks	Concentration: 90% of saturation solubility in distilled water.
Test Facility	CRL (2017a)

Flash Point 106 °C at 100.7 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Close cup method
Test Facility	CRL (2017a)

Autoignition Temperature 230 °C at 102.2 – 102.38 kPa

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

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Based on the chemical structure
Test Facility CRL (2017a)

Oxidizing Properties Predicted negative

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks Based on the chemical structure
Test Facility CRL (2017a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Wistar
Vehicle	None
Remarks – Method	No significant protocol deviations

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Hunched posture, uncoordinated movements and piloerection were observed for all animals on Day 1.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks – Results	The animals showed expected body weight gains during the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	CRL (2017b)

B.2. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test
Species/Strain	Rat/Wistar
Vehicle	None
Type of dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 M/5 F	2,000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity – Local	No local effects were noted.
Signs of Toxicity – Systemic	Chromodacryorrhoea (snout) was noted for one male between Days 2 and 4 and three females on Day 1.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks – Results	The animals showed expected body weight gains during the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	CRL (2017c)

B.3. Acute Inhalation Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity

Species/Strain	Rat/Wistar
Vehicle	None
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	3.5 – 3.7 µm Mass Median Aerodynamic Diameter
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	3 M/3 F	7.2	5	0/6
2	2 M/2 F	6.8	5.1	0/4

LC50	> 5 mg/L/4 hours
Signs of Toxicity	Slow breathing was noted during exposure and lethargy, hunched posture, laboured respiration, chromodacryorrhea (nose) and ptosis were noted for the animals on Days 1 and/or 2 after exposure.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks – Results	The animals showed expected body weight gains, except for one female which showed body weight loss up to Day 8. This animal regained weight during the second week.

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

TEST FACILITY CRL (2017d)

B.4. Skin Corrosion – *In Vitro* Human Skin Model

TEST SUBSTANCE Notified chemical

METHOD OECD TG 431 *In vitro* Skin Corrosion – Human Skin Model Test

Vehicle	None
Remarks – Method	No significant protocol deviations. The EpiDerm test system was used.

Results

Test Material	*Mean OD_{570} of Triplicate Tissues*		*Relative Mean Viability (%)*		*SD of Relative Mean Viability*	
	3 minute exposure	60 minute exposure	3 minute exposure	60 minute exposure	3 minute exposure	60 minute exposure
Negative control	1.556	1.742	100.0	100	3.7	0.5
Test substance	1.492	1.692	96	97	26	0
Positive control	0.142	0.137	9.1	7.9	16	4.6

OD = optical density; SD = standard deviation

Remarks – Results

The preliminary test indicated that the test substance did not directly reduce MTT.

The relative mean viabilities of the test substance treated tissues were 96% and 97% after 3 and 60 minute exposure periods, respectively. A mean tissue viability of ≥ 50% (for 3 minute exposure) and ≥ 15% (for 60 minute exposure) is considered to be non-corrosive.

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

CONCLUSION	The notified chemical was considered to be non-corrosive to the skin under the conditions of the test.
TEST FACILITY	CRL (2017e)

B.5. Skin Irritation – *In Vitro* Human Skin Model

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method
Vehicle	None
Remarks – Method	No significant protocol deviations. The EpiSkin-SM test system was used.

RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	0.734	100	5.9
Test substance	0.570	78	5.8
Positive control	0.157	21	11

OD = optical density; SD = standard deviation

Remarks – Results	The preliminary test indicated that the test substance did not directly reduce MTT. The relative mean tissue viability for the test substance as compared to the negative control was 78%. As the relative mean tissue viability for the test substance was above 50%, it is considered to be non-irritating. The positive and negative controls gave satisfactory results, confirming the validity of the test.
CONCLUSION	The notified chemical was considered to be non-irritating to the skin under the conditions of the test.
TEST FACILITY	CRL (2017f)

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

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants
Vehicle	None
Remarks – Method	No significant protocol deviations

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues (SD)*	*Mean Permeabilities of Triplicate Tissues*	*IVIS*
Vehicle control	0.1	0.005	0.1
*Test substance**	-0.1	0.011	0
*Positive control**	19	1.992	48.9

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

Remarks – Results	The IVIS of the test substance was 0.0. An IVIS ≤ 3 is considered as not requiring classification for eye irritation. The negative and positive controls gave satisfactory results confirming the validity of the test system.
CONCLUSION	The notified chemical was not considered an eye irritant under the conditions of the test.
TEST FACILITY	CRL (2017g)

B.7. Skin Sensitisation – LLNA

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone:olive oil (4:1)
Preliminary study	Yes
Positive control	Conducted in parallel with the test substance using α-hexylcinnamaldehyde.
Remarks – Method	No significant protocol deviations. A preliminary test was conducted using undiluted test substance to justify the concentrations for the main study.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	5 F	748.95	-
25	5 F	880.80	1.18
50	5 F	1245.17	1.66
100	5 F	2809.55	3.75
Positive Control			
25	5 F	3643.43	4.87

EC3	82%
Remarks – Results	No unscheduled mortalities or signs of systemic toxicity were observed during the study period. The stimulation index was > 3 in the high dose test group, indicating a sensitising response. The EC3 was calculated to be 82%. Body weight changes of the test animals were comparable to that observed in the vehicle control group.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Envigo (2017c)

B.8. Skin Sensitisation – Human Volunteers

TEST SUBSTANCE	Notified chemical (10%)
METHOD	Repeated insult patch test with challenge
Study Design	Induction procedure: patches containing 0.15 mL of the test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications during the induction period. Patches were removed

	by the subjects after 24 hours and graded by technicians after an additional 24 hours (or 48 hours for patches applied on Friday). Rest period: ~10-21 days Challenge procedure: Patches were applied to a naïve site. The sites were scored 24, 48 and 72 hours after application. If reactions were observed at the 72 hour observation, these were re-evaluated at 96 hours.
Study Group	83 F, 31 M; age range 18 - 70 years
Vehicle	Ethanol:diethyl phthalate (25:75)
Remarks – Method	Occluded. The test substance was spread on a 3.63 cm^2 patch.

RESULTS

Remarks – Results	102/114 subjects completed the study. Twelve subjects discontinued with the study for reasons unrelated to the test substance. No adverse events were noted during the study.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories (2018)

B.9. Repeat Dose Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/Wistar
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	SDS rat and mouse No.1 maintenance diet
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose ppm (mg/kg bw/day M/F)*	*Mortality*
Control	5 per sex	0	0/10
Low Dose	5 per sex	1400 (96)/(94)	0/10
Mid Dose	5 per sex	4200 (307)/(280)	0/10
High Dose	5 per sex	12500 (917)/(869)	0/10
Control Recovery	5 per sex	0	0/10
High Dose Recovery	5 per sex	12500 (917)/(869)	0/10

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

No clinical signs of systemic toxicity were noted. There were no treatment-related changes in the behavioural parameters and sensory reactivity and no toxicologically significant changes in functional performance.

Body weight gain was slightly low during the 1st week in both sexes of the high dose group and was higher than the controls during the 1st week of recovery in both sexes which had previously received this dietary concentration. Food consumption was low during the 1st four days in both sexes of the high dose group and was slightly higher than controls during the recovery period in males which had previously received this dietary concentration. A visual assessment of water intake did not reveal any test substance-related effects.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Chemistry

A dose-related reduction of glucose concentration (down to 0.6 × Control) was noted in all treated groups of males but this finding showed full recovery. Findings which had a doubtful/uncertain relationship to the test substance included high albumin concentration (1.06 × Control) in all treated groups of males (with a slight increase in albumin to globulin ratio in the high dose group) and slightly high phosphorus concentration (up to 1.3 X Control) in all treated groups of females. These findings were considered slight, non-adverse and disappeared after recovery.

Haematology
Slightly high neutrophil counts (1.4 × Control) were noted in males of the high dose group and slightly high lymphocyte (1.3 × Control) and monocyte (1.7 × Control) counts and slight increase (1.3 × Control) in total white blood cell counts were noted in females of the high dose group. The findings in females showed complete recovery but neutrophil counts remained slightly high (1.6 × Control) in males after recovery. Hematological findings which had a doubtful/uncertain relationship to the test substance included slightly low reticulocte counts (down to 0.8 × Control) in all treated groups of males and slightly high red cell distribution width (1.1 × Control) in females of the high dose group. These findings were considered slight, non-adverse and disappeared after recovery.

Urinalysis
Slightly low urinary volume (0.5 × Control) in males of the mid and high dose groups was noted but showed full recovery.

Effects in Organs

Organ weights
Slightly high adjusted kidney weights (maximum 1.1 × Control) were noted in all treated groups of males, without apparent evidence of recovery or progression (in terms of the magnitude of change from controls) after recovery. Slightly high adjusted liver weights (1.1 × Control) were noted in females of the high dose group, with evidence of recovery. Slightly low adjusted ovary and uterus weights (0.7 and 0.6 × Control, respectively) were noted in females of the high dose group, with complete or partial recovery. With the exception of the slight increase in kidney weights in males, none of the other changes in organ weight were associated with any test substance-related histopathological changes.

Necropsy
No adverse effects were noted at necropsy.

Histopathology
An increased incidence and severity (minimal/slight severity) of hyaline droplet accumulation was evident at all dose groups and occurred with tubular basophila (minimal severity) in two males of the mid and high dose groups respectively, with evidence of partial recovery for the hyaline droplet accumulation by the end of the recovery period. However, the incidence and severity of the basophilia finding had shown some progression (5/5 males of the high dose group showed minimal or slight severity at the end of the recovery period). There was no evidence of any adverse/degenerative renal pathology in this study.

Remarks – Results
It was concluded by the study authors that the kidney was a potential target organ in the male rat but there was no evidence of any adverse/degenerative renal pathology. Consequently, the No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 12500 ppm, the highest level tested.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 12500 ppm (equivalent to approximately 917 and 869 mg/kg/day in males and females, respectively) in this study.

TEST FACILITY	Envigo (2017d)

B.10. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	Test 1: a) With metabolic activation: 1.5 - 5000 µg/plate b) Without metabolic activation: 1.5 - 5000 µg/plate Test 2: a) With metabolic activation: 1.5 - 5000 µg/plate b) Without metabolic activation: 0.5 - 5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks – Method	Positive controls: With metabolic activation: 2-aminoanthracene (TA1535, TA1537, TA100, WP2uvrA); benzo(a)pyrene (TA98) Without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine [TA1535, TA100, WP2uvrA]; 9-aminoacridine (TA1537); 4-nitroquinoline-1-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	Not tested	≥ 500	> 5000	negative
Test 2	Not tested	≥ 500	> 5000	negative
Present				
Test 1	Not tested	≥ 1500	> 5000	negative
Test 2	Not tested	≥ 1500	> 5000	negative

Remarks – Results	No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with the test substance at any dose level, with or without S9-mix. Vehicle and positive controls performed as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Envigo (2017e)

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

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks – Method	The dose selection for the main experiments was based on toxicity of a preliminary test carried out at 7 – 1840 µg/mL. Positive controls were cyclophosphamide and mitomycin C.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 115, 230, 460, 575*, 690*, 920*, 1840	4 h	24 h
Test 2	0*, 115, 230, 460, 690*, 920*, 1150*, 1840	24 h	24 h
Present			
Test 1	0*, 57.5*, 115*, 230*, 345, 460, 690, 920	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	≥ 920	≥ 920	≥ 920	negative
Test 2	≥ 920	≥ 230	≥ 690	negative
Present				
Test 1	≥ 1840	≥ 1840	≥ 1840	negative

Remarks – Results

Hemolysis (an indication of a toxic response to the erythrocytes and not indicative of any genotoxic response to the lymphocytes) was observed at ≥ 57.5 µg/mL in all exposure groups in the preliminary test.
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 peripheral lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Envigo (2017f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

Different results were reported for the TG 310 and TG 301F biodegradability study reports. However, the TG 310 study relies on total inorganic carbon analysis, which assumes complete mineralisation to CO_2. The study indicates that the notified chemical degrades but complete mineralisation had not occurred at day 28 to a sufficient amount to demonstrate that the notified chemical is readily biodegradable. The TG 301F study relies on biological oxygen demand which includes biodegradation where the notified chemical is converted to oxidised species, but not CO_2. The notified chemical may oxidise to such species. Therefore, the biodegradability of the notified chemical was based on the results from the TG 301F study report.

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310 Ready Biodegradability: CO_2 in sealed vessels (Headspace test)
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Total inorganic carbon (TIC)
Remarks - Method	The test substance was added to the mineral medium to give a final organic carbon concentration of 20 mg C/L. The organic carbon content was based on the molecular formula. Biodegradation (mineralization to CO_2) was determined by measuring the net increase in total inorganic carbon levels over time.

RESULTS

Test substance		*1-Octanol*	
Day	*% Degradation*	*Day*	*% Degradation*
7	2	7	83
14	4	14	105
21	30	21	ND
28	46	28	96

ND= not determined

Remarks - Results	The reference compound 1-octanol reached the pass level of biodegradation by day 5 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation showing toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 46%.
CONCLUSION	The notified chemical is not readily biodegradable; however, the study indicates inherent of degradability.
TEST FACILITY	CRL (2017h)

C.1.2. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from a municipal STP
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD, Automatic respirometer
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was directly added to the test medium.

RESULTS

Test Substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	21.5	7	58.9
14	63.4	14	85.3
21	74.6	21	97.3
28	82.1	28	99.0

Remarks – Results: All validity criteria for the test were satisfied. The total oxygen intake in the inoculum blank was 26.1 mg O_2/L at the end of the study. The pH during the test was maintained between 6.86 and 7.65. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The biodegradation of the reference substance, aniline, reached 85.3% at 14 days. The degree of degradation of the test substance after 28 days was 82.1%. The 10-d window was passed.

CONCLUSION: The notified chemical is readily biodegradable.

TEST FACILITY: NIES (2017a)

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: Rare minnow (*Gobiocyprus rarus)*
Exposure Period: 96 hours
Auxiliary Solvent: None
Water Hardness: 166 - 174 mg $CaCO_3$/L
Analytical Monitoring: TOC
Remarks – Method: The definitive test was designed based on the preliminary test results. No major deviations from the test guidelines was reported. The test substance was directly added to the test solution. The test solution was renewed daily.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Mortality*			
Nominal	*Measured*		*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0
10	10.3	10	0	0	0	0
20	20.3	10	0	0	0	0
40	39.9	10	1	2	3	3
60	59.3	10	2	4	5	7
80	80	10	5	10	10	10
100	97.5	10	10	10	10	10

LC50: 46.0 mg/L (95%CL of 38.2 – 55.3 mg/L) at 96 hours
Remarks – Results: All validity criteria for the test were satisfied. The dissolved oxygen was 85 - 95% during the test. The pH was maintained between 6.0 and 8.5. The analysed test substance concentration during the test was within ± 20% of the nominal concentration so the results are based on the analytically confirmed concentrations.

CONCLUSION: The notified chemical is harmful to fish.

TEST FACILITY NIES (2017b)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test – 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	140 mg $CaCO_3$/L
Analytical Monitoring	GC/MS
Remarks – Method	The definitive test was designed based on the preliminary test results. No major deviations from the test guidelines was reported. A stock solution of the test substance (120 mg/L) was prepared in test water and stirred for 15 minutes. This was then used to prepare the required nominal concentrations for the definitive test. The test solutions were renewed daily. The test solutions were sampled at the start (0 and 24 hours) and the end of the exposure intervals (24 and 48 hours) for analysis.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*% Immobilised*	
Nominal	*Initial Measured*		*24 h*	*48 h*
Control	Control	20	0	0
7.5	8.2	20	0	0
15	13	20	0	7
30	24	20	0	3
60	47	20	0	7
120	108	20	2	16

EC50	61 mg/L (95% CL of 8.2 – 108) at 48 hours (calculated using Binomial analysis)
Remarks – Results	All validity criteria for the test were satisfied. Since the nominal concentrations were outside the 80 – 120 % range as recommended by the guidelines, the results are based on the mean measured concentrations. The dissolved oxygen was > 89% of saturation.

CONCLUSION The notified chemical is harmful to aquatic invertebrates.

TEST FACILITY EAG (2017)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
EC Council Regulation No 440/2008 C.3 Algal Inhibition Test

Species	*Raphidocelis subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: Control, 6.3, 13, 25, 50, 100 mg/L Geometric mean measured: Control, 3.1, 6.8, 15, 36, 77 mg/L
Auxiliary Solvent	None
Water Hardness	50.3 Ca+Mg/L
Analytical Monitoring	HPLC – DAD
Remarks – Method	The definitive test was designed based on the preliminary test results. No major deviations from the test guidelines was reported. The test substance

was directly added to test water and stirred for 3.5 hours before testing. The test solutions were sampled at the start and after 72 hours for analysis of the test substance. An abiotic control was also run for analytical purposes.

RESULTS

Biomass		*Growth*	
EyC50 (mg/L at 72 h)	*NOEC (mg/L)*	*ErC50 (mg/L at 72 h)*	*NOEC (mg/L)*
22 (95% CL of 20 - 24)	6.8	55 (95% CL of 53 - 57)	6.8

Remarks – Results

All validity criteria for the test were satisfied. The mean cell density in the control increased 148 times after 72 hours. The mean coefficient of variation for section by section specific growth was 29.8%. The coefficient of variation for mean average specific growth in the control replicate was 1.6%. The analysed test substance concentration during the test declined substantially, including in the abiotic control during the test exposure period. Therefore, the results are based on geometrical mean measured concentrations. The calculation of cell densities, growth rates, yields and percent inhibition values, as well as all statistical analyses, were conducted using "The SAS System for Windows," Version 8.2.

CONCLUSION

The notified chemical is harmful to algae.

TEST FACILITY

EAG (2018)

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