File No: LTD/1994

November 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclopentanol, 1-ethyl-2-(3-methylbutyl)-

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/1994	International Flavours and Fragrances (Australia) Pty Ltd	Cyclopentanol, 1-ethyl-2-(3-methylbutyl)-	Yes	≤ 1 tonne per annum	Component of cosmetic and household products

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Serious eye damage/eye irritation (Category 2)	H319 – Causes serious eye irritation

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

Hazard classification	*Hazard statement*
Acute Category 2	H401 - Toxic to aquatic life

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:
  – Serious Eye damage/Eye irritation (Category 2): H319 – Causes serious eye irritation

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

CONTROL MEASURES

Occupational Health and Safety

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

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation processes:
  - Coveralls, impervious gloves, goggles

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical 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;

or

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

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

Safety Data Sheet
The SDS of the notified chemical and products 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
International Flavours and Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

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

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

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China (2014)
USA (2016)

2. IDENTITY OF CHEMICAL

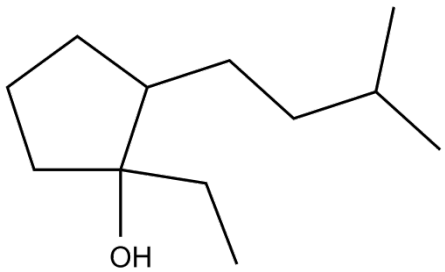
MARKETING NAME(S)
Pamplezest

CAS NUMBER
1465004-85-6

CHEMICAL NAME
Cyclopentanol, 1-ethyl-2-(3-methylbutyl)-

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

STRUCTURAL FORMULA



MOLECULAR WEIGHT
184.32 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
96.9% (typically > 90%)

The notified chemical is a racemic mixture with the following composition:

Cyclopentanol, 1-ethyl-2-(3-methylbutyl)-, (1*R*,2*R*)-*rel*- (91.8%)
Cyclopentanol, 1-ethyl-2-(3-methylbutyl)-, (1*S*,2*R*)-*rel*- (5.1%)

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

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

Chemical Name	Cyclopentanone, 2-(3-methylbutyl)-		
CAS No.	16425-04-0	*Weight %*	2 (typically < 7%)

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear liquid

Property	Value	Data Source/Justification
Freezing Point	< -30 °C	Measured
Boiling Point	235 °C at 101.8 kPa	Measured
Density	874 kg/m^3 at 20 °C	Measured
Vapour Pressure	7.45 x 10^{-2} kPa at 20 °C	Measured
Water Solubility	0.257 g/L at 20 °C	Measured. Due to the structure of the molecule it is expected to be less water soluble, but micro-emulsions could have affected measured outcomes. See also partition coefficient and surface tension studies.
Hydrolysis as a Function of pH	Not determined	The notified chemical does not contain functional groups or substructures that are susceptible to hydrolysis. Therefore, hydrolysis was not measured or estimated.
Partition Coefficient (n-octanol/water)	log Pow = 2.4 at 20 °C	Measured. A whitish layer observed at the octanol-water interface indicates the chemical is possibly surface active.
Surface Tension	52.0 mN/m at 20 °C	Measured. The measured value is < 60 mN/m, and hence is indicative of potential surface activity.
Adsorption/Desorption	log K_{oc} = 2.31 – 2.85 at 25 °C	Measured
Dissociation Constant	Not determined	The notified chemical does not contain functionality that is expected to dissociate under environmental conditions
Flash Point	101 ± 2 °C at 101.3 kPa	Measured
Flammability	Not pyrophoric	Measured
Autoignition Temperature	274 ± 5 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Predicted negative	Estimated

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is 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 not be manufactured in Australia. The notified chemical will be imported into Australia as a component of fragrance preparations (at concentrations ≤ 10%).

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

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

PORT OF ENTRY
Melbourne

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

TRANSPORTATION AND PACKAGING
The notified chemical may be imported into Australia as a component of fragrance preparations (at concentrations ≤ 10%) in 208 L polypropylene-lined steel drums. End-use products containing the notified chemical (at concentrations ≤ 1.25%) will be in packaging suitable for retail sale.

USE
The notified chemical will be used as an ingredient in cosmetic and household products. The concentration of the notified chemical in final consumer products will vary but the proposed usage concentrations will not exceed 1.25%.

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging of the notified chemical will occur at the notifier's facility. Imported products containing the notified chemical (at concentrations ≤ 10%) will be stored at this facility until they are transported to customer facilities (in original importation packaging) for reformulation into consumer products.

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

End-use
Household products
Household products containing the notified chemical (≤ 1.25% concentration) may be used by consumers and professional workers (such as cleaners). The products may be used in either closed systems or open manual processes including rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 1.25% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Mixing and compounding	4	250
Drum handling and maintenance	1 - 2	200 - 250
Plant operator - equipment maintenance	2	250
Quality control	1	250
Professional user – hairdressers, cleaners etc.	8	250

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of fragrance preparations (at concentrations ≤ 10%) or as a component of end-use products (at concentrations ≤ 1.25%) only in the event of accidental rupture of containers. The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective coveralls, chemical resistant gloves and safety glasses.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 10% concentration) may occur during weighing and transfer stages, blending, quality control analysis, packaging of materials and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of PPE such as coveralls, goggles and impervious gloves, and adequate local ventilation or self-contained breathing apparatus as required.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at ≤ 1.25% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use PPE to minimise repeated exposure, but use is not always expected. However, the notifier states that good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the finished products containing the notified chemical.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical through the use of a wide range of cosmetic and household products (at ≤ 1.25% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if the products are applied by spray.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 4.97 mg/L/4 hour; low toxicity
Skin corrosion (*in vitro*) - EPIDERM™ human skin model	non-corrosive
Skin irritation (*in vitro*) - EPISKIN™ reconstructed human epidermis model	non-irritating
Rabbit, skin irritation	irritating
Eye irritation (*in vitro*) - Bovine corneal opacity and permeability test	no prediction can be made
Eye irritation (*in vitro*) - Human cornea model test	irritating
Skin sensitisation (*in chemico*) – Direct peptide reactivity assay	not a category 1 skin sensitiser
Skin sensitisation (*in Vitro)*: ARE-Nrf2 luciferase test method	not a category 1 skin sensitiser
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation at 50% concentration
Human, skin sensitisation – RIPT (5%)	no evidence of sensitisation
Rat, combined repeated dose (dietary) with reproductive and developmental toxicity screening test	NOAEL(parental and repro/develop) females > 328 mg/kg bw/day; males > 265 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test in human lymphocytes	non genotoxic

Toxicokinetics, metabolism and distribution

No toxicokinetic data on the notified chemical were submitted. For dermal and gastrointestinal absorption, molecular weights below 100 g/mol are favourable for absorption and molecular weights above 500 g/mol do not favour absorption (ECHA, 2014). Dermal uptake is likely to be moderate to high if the water solubility is between 100 – 10,000 mg/L. Dermal uptake through the epidermis is expected if the partition coefficient (log P) values are between -1 and 4 (ECHA, 2014). Gastrointestinal absorption and absorption across the respiratory tract are also likely to be high if the partition coefficient (log P) values are between -1 and 4. Absorption of the notified chemical through the skin, gastrointestinal tract and respiratory tract is expected based on the partition coefficient (2.4), water solubility (257 mg/L) and moderately low molecular weight (184.32 g/mol).

Acute toxicity

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

In an acute inhalation toxicity study, animals were exposed to an aerosol atmosphere of the notified chemical of 4.97 mg/L. All animals exhibited hunched posture and/or decreased respiratory rate, noisy respiration and piloerection as well as instances of laboured respiration, ataxia, lethargy, chromodacryorrhea and dehydration. Recovery was observed in all animals between six to eight days after exposure. Dark and/or pale patches on the lung were observed in four animals (1/5 male and 3/5 females). There were no unscheduled deaths.

Irritation

The notified chemical was slightly irritating to the skin but not corrosive based on *in vitro* studies. Under the conditions of the EpiSkin model, the relative mean tissue viability of the test substance compared to the negative control was 50.6%, indicating a negative result for skin irritation. However, while the chemical does not meet the criteria for classification, it cannot be excluded from having the potential to cause some skin irritation. Studies performed on rabbits indicated that the notified chemical was slightly irritating to the skin, with animals exhibiting well-defined erythema and slight oedema, as well as a loss of skin elasticity. Full recovery was observed by the end of the observation period. The effects were sufficient to classify it as Skin Corrosion/Irritation (Category 3) under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*, however category 3 skin irritants are exempted from the hazardous chemical definition under Model Work Health and Safety Regulations in Australia (SWA, 2016).

The notified chemical was irritating to the eye based on an *in vitro* study conducted on a human cornea model with the potential to cause serious eye damage or irritation. An *in vitro* study conducted on bovine corneas indicated that the notified chemical did not cause serious eye damage. When considered together, the notified chemical is expected to have the potential to cause serious eye irritation.

Sensitisation
A battery of tests consisting of one *in chemico* and one *in vitro* assay were conducted to evaluate the sensitisation potential of the notified chemical. The tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD, 2012). The tests are thus considered relevant for assessment of the skin sensitisation potential of the notified chemical.

The molecular initiating event in the AOP for sensitisation is the covalent binding to nucleophilic centres in skin proteins. The *in chemico* Direct Peptide Reactivity Assay (DPRA) measures the interaction of a test substance with cysteine and lysine containing small synthetic peptides (representing the nucleophilic centres in skin protein). Thus, the assay is proposed to address the molecular initiating event.

The first key event in the AOP for sensitisation is the activation of keratinocytes which leads to upregulation of stress related proteins (cytokines) via transcriptional upregulation of the genes. The Keratinocyte ARE- Reporter Cell Line KeratinoSens Assay measures change in expression of luciferase gene under the transcriptional control of a constitutive promoter fused with an Antioxidant Response Element (ARE) from a gene that is known to be upregulated by contact sensitisers. Hence the assay addresses the second key event in the AOP for sensitisation.

The notified chemical showed a negative response in both of the above sensitisation tests suggesting the notified chemical is not a skin sensitiser.

Sensitising effects were not observed in a local lymph node assay or in a human repeated-insult patch study (at 5% concentration) following exposure to the notified chemical.

Repeated dose toxicity
In a combined repeated dose (dietary) toxicity study with the reproduction/developmental toxicity screening test in rats, the No Observed Adverse Effect Level (NOAEL) for parental and reproductive and developmental toxicity was established as > 328 mg/kg bw/day for females and > 265 mg/kg bw/day for males based on absence of adverse effects in animals exposed to the highest dose tested (≥ 4,500 mg/kg diet).

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

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

Hazard classification	*Hazard statement*
Serious Eye damage/Eye irritation (Category 2)	H319 – Causes serious eye irritation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is expected to be an eye irritant and also a mild skin irritant. The notified chemical is expected to have low systemic toxicity based on the absence of adverse effects in animal studies.

Transport, Storage and Reformulation
Exposure of workers to the notified chemical (at ≤ 10% concentration) may occur during transport and blending operations. The notified chemical is considered to be irritating. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

Provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE (impervious gloves, goggles, coveralls, and respiratory protection), 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 ≤ 1.25 % concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health
Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products (at ≤ 1.25% concentration in individual products). The main route of exposure is expected to be dermal, while ocular and inhalation exposure are also expected where products are applied by spray.

The notified chemical is an eye irritant and a mild skin irritant. Given the low proposed end use concentrations in cosmetic and household products irritant effects are not expected.

Based on the results from of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test showing no adverse effects up to the highest dose tested (≥ 4,500 mg/kg in the diet), systemic effects from repeated exposure to the notified chemical are not expected.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 1.25% concentration in cosmetic and household products is not considered 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 as a component of fragrance oil formulations for local reformulation into finished cosmetics, soaps, detergents, household cleaners and other consumer 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. The process is expected to be followed by automated filling of the formulated products into containers of various sizes suitable for retail sale and end-use. Wastes containing the notified chemical generated during reformulation include equipment wash water, empty import containers and spilt materials. These will be collected, recycled or released to on-site wastewater treatment facilities or sewers in accordance with local government regulations. Empty containers will be either recycled or disposed of to landfill.

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.

RELEASE OF CHEMICAL FROM DISPOSAL
Approximately 1% of the import volume of the notified chemical is expected to remain as residues in end-use containers (or up to 10 kg/yr). Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate
Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. For details

of the environmental fate studies, please refer to Appendix C. Based on the result of the biodegradability study, the notified chemical is not considered to be readily biodegradable (1% in 28 days). Hydrolysis was not determined by measurement because the notified chemical does not contain functional groups or substructures that are susceptible to hydrolysis.

The half-life of the notified chemical in air due to reaction with hydroxyl radicals was estimated as 6 hours. [AopWin (v1.92)]. Therefore, in the event of release to the atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

In sewage treatment plants (STPs) a significant proportion of the notified chemical may partition to the water phase, based on its moderate water solubility (measured water solubility 257 mg/L; including micro-emulsions) and low soil adsorption coefficient (log K_{OC} = 2.31 – 2.85 mL/g) and be released to surface water. However, a proportion of the notified chemical may partition to sludge based on its potential surface activity.

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 high mobility based on its low soil adsorption coefficient. However, the notified chemical has low potential to bioaccumulate based on its n-octanol-water partition coefficient (log P_{OW} < 4.2).

In aquatic and soil compartments, the notified chemical is expected to degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

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 0.562 µg/L may potentially result in a soil concentration of approximately 3.745 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 18.73 µg/kg and 37.45 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 2.466 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 = 8.2 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	72 h ErC50 = 9.3 mg/L 72 h NOEC = 1.3 mg/L	Toxic to algae
Inhibition of Bacterial Respiration	3 h IC50 = 520 mg/L	Not inhibitory to microbial activity

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be toxic 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 2: Toxic to aquatic life". On the basis of acute toxicity data, NOEC value and ready biodegradability criteria, the notified chemical is not subject to GHS chronic classification for substances hazardous to the aquatic environment.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated from the most sensitive endpoint (NOEC) for algae. An assessment factor of 100 was used given three acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Algae)	1.3	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	13	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	13	0.043
Q - Ocean	0.06	13	0.004

The Risk Quotients (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemical have 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 readily biodegradable, but is not considered to have bioaccumulation potential. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < - 30 °C

Method	EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Temperature controlled, jacketed glassware with a temperature range of – 30 °C to 150 °C used. No freezing was observed after approximately 40 minutes at – 30 °C.
Test Facility	Chilworth (2014)

Boiling Point 235 °C at 101.8 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Differential scanning calorimetry.
Test Facility	Envigo (2016)

Density 874 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Pycnometer.
Test Facility	Envigo (2016)

Vapour Pressure 0.0745 kPa at 20 °C

Method	EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Static method (U-tube manometer apparatus).
Test Facility	Chilworth (2014)

Water Solubility 0.257 g/L at 20 °C

Method	EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method. Due to the nature of the test material, the influence of micro-emulsion must be considered when interpreting the estimated solubility result.
Test Facility	Chilworth (2014)

Partition Coefficient (n-octanol/water) log Pow = 2.4 at 20 °C

Method	EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Shake Flask Method. A whitish layer was observed at the octanol/water interface. Possible sample loss at the octanol-water interface must be considered when interpreting the test result.
Test Facility	Chilworth (2014)

Surface Tension 52.0 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Ring method. Concentration: 90% saturated in water (1.25 mg/mL). As this chemical was surface active this may have added uncertainty to the study results.
Test Facility	Envigo (2016)

Adsorption/Desorption log K_{oc} = 2.31 – 2.85 at 25 °C

Method	OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method
Remarks	Gas chromatography with flame ionization detector (GC-FID) was used for analysis of notified chemical.
Test Facility	Envigo (2017a)

Flash Point 101 ± 2 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point OCSPP Guidelines Method 830.6315
Remarks	Closed cup.
Test Facility	Envigo (2016b)

Flammability Non-pyrophoric

Method	EC Council Regulation No 440/2008 A.13 Pyrophoric Properties of Solids and Liquids
Remarks	A sample of the notified chemical was added to diatomaceous earth. Observation period for onset of ignition was 5 minutes. Six duplicate tests were performed. Notified chemical was added to dried filter paper, with an observation period for onset of ignition of 5 minutes. Three duplicate tests were performed. No ignition, fumes or charring were observed in any of the tests conducted
Test Facility	Envigo (2016b)

Autoignition Temperature 274 ± 5 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Carbolite flask heater
Test Facility	Envigo (2016b)

Oxidizing Properties

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks	Predicted to be negative based on the chemical structure not having any structural alerts that would imply oxidising properties.
Test Facility	Envigo (2016b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity - Fixed Dose Method EC Directive 92/69/EEC B.1bis Acute Toxicity (Oral) Fixed Dose Method
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	Arachis oil BP
Remarks - Method	GLP compliant. No deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	300	0/1
2	1 F	2000	0/1
3	4 F	2000	0/4

Discriminating Dose	> 2,000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were observed in the animal exposed to the low-dose of the test substance Hunched posture, lethargy, and ataxia or pilo-erection were observed in 3/5 animals in the high-dose groups, 4 hours after exposure. Hunched posture persisted in 1 animal at the 24 hour observation, with all animals showing recovery at the 48 hour observation. No signs of systemic toxicity were observed in 2/5 animals in the high-dose group.
Effects in Organs	No abnormalities were recorded.
Remarks - Results	All animals made the expected body weight gains.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Envigo (2017b)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	None.
Type of dressing	Semi-occlusive.
Remarks - Method	GLP compliant. No deviations from the study protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 M	2000	0/5
2	5 F	2000	0/5

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema was recorded in 3/5 females 24 hours after exposure. All animals had recovered by the 48 hour observation. No other signs of irritation were recorded.
Signs of Toxicity - Systemic	None.

Effects in Organs	None detected.
Remarks - Results	All animals made the expected body weight gains
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Envigo (2017c)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation)
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	None.
Method of Exposure	Oro-nasal exposure
Exposure Period	4 hours
Physical Form	Solid aerosol (particulate).
Particle Size	3.09 µm (mass median aerodynamic diameter)
Remarks - Method	GLP compliant. No significant deviations from the study protocol. Inhalable fraction (< 4 µm) – 61.5%

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	5 M, 5 F	10.87	4.97 ± 0.20	0/10

LC50	> 4.97 mg/L/4 hours
Signs of Toxicity	All animals exhibited wet fur and decreased respiratory rate during the exposure period, as well as hunched posture and pilo-erection for up to an hour following the exposure period. Ataxia was also observed in 4/5 males and 2/5 females, and ataxia with lethargy was observed in 1/5 males and 3/5 females. On the first day of the recovery period, hunched posture was observed in all animals with some animals also exhibiting piloerection (1/5 males, 1/5 females), decreased respiratory rate (4/5 males, 1/5 females), noisy respiration (2/5 males, 1/5 females), and red-brown staining around the eyes (1/5 males). Laboured respiration, ataxia, lethargy, chromodacryorrhea and dehydration were also observed (1/5 females). All animals continued to exhibit hunched posture on days 2, 3 and 4, with recovery from other effects indicated (piloerection in 1/5 males and 1/5 females on day 2 only; noisy respiration in 2/5 males on day 2 and 3, and 1/5 males on day 3; decreased respiratory rate in 1/5 males on day 2 and 3). Sneezing in 4/5 males, 5/5 females was observed on day 2 and 3 of the recovery period, with recovery indicated on day 4 (1/5 males, 1/5 females). However, all animals exhibited sneezing on Day 5. Recovery from all effects was indicated over days 6 (all females and 3/5 males) and 7 (1/5 males), with full recovery of all animals recorded on day 8 of the recovery period. No other effects were recorded for the remainder of the recovery period.
Effects in Organs	Four animals (1/5 male, 3/5 females) exhibited dark or pale patches on the lung, with one of the female animals exhibiting dark and pale patches. No other abnormalities were detected.
Remarks - Results	Following exposure, all animals showed a loss in body weight on the first

day, with 2/5 males and 2/5 females exhibiting no body weight gain or a loss in body weight from days 1 to 3. All males and 4/5 females made body weight gains over the reminder of the recovery period. One female gained weight over days 3 to 7, but then made no gains over days 7 to 14.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY Envigo (2017d)

B.4. Irritation – skin (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test
EC Council Regulation No 440/2008 B.40 BIS. *In vitro* Skin Corrosion - Human Skin Model Test
EpiDerm™ Reconstructed Human Epidermis Model

Vehicle None.

Remarks - Method GLP compliant.
No deviations from protocol.

Negative control: Sterile distilled water.
Positive control: 8 N Potassium hydroxide.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues (± SD)*		*Relative mean viability (%)*	
	3 min exposure	*60 min exposure*	*3 min exposure*	*1 hour exposure*
Negative control	1.656 (± 0.073)	1.596 (± 0.114)	100	100
Test substance	2.110 (± 0.013)	1.969 (± 0.069)	127.4	123.3
Positive control	0.091 (± 0.008)	0.087 (± 0.018)	5.5	5.4

OD = optical density; SD = standard deviation

Remarks - Results The positive and negative controls performed as expected.

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

TEST FACILITY Envigo (2016c)

B.5. Irritation – skin (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method
EC Council Regulation No 440/2008 B.46 BIS. *In vitro* Skin irritation - Human Skin Model Test
EpiSkin™ Reconstituted Human Epidermis Model

Vehicle None.

Remarks - Method GLP compliant.
No deviations from protocol.

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

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*

Negative control	0.845	100	0.047
Test substance	0.428	50.6	0.022
Positive control	0.086	10.1	0.011

OD = optical density; SD = standard deviation

Remarks - Results

The positive and negative controls performed as expected.

The relative mean tissue viability of the test substance compared to the negative control was 50.6%. A value above 50% indicates a negative result for skin irritation. However, as the result is on the threshold the test substance cannot be excluded from having the potential to cause some skin irritation.

CONCLUSION

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

TEST FACILITY

Envigo (2017e)

B.6. Irritation – skin

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 404 Acute Dermal Irritation/Corrosion
EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation)

Species/Strain: Rabbit/New Zealand White
Number of Animals: Two
Vehicle: None
Observation Period: 14 days
Type of Dressing: Occlusive
Remarks - Method: GLP compliant.
No deviations from protocol.

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Erythema/Eschar	2	2	2	< 14 days	0
Oedema	2	2	2	< 14 days	0

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

Remarks - Results

Both animals exhibited well-defined erythema and slight oedema immediately following exposure persisting to the 72 hour observation. Post exposure, a loss of skin elasticity was observed in both animals at the 24, 48 and 72 hour observations as well as a loss of skin flexibility (72 hour observation).

One animal exhibited no erythema or oedema at the day 7 observation, although moderate desquamation was observed. The remaining animal exhibited crust formation which prevented evaluation of any persistent erythema.

Both animals had fully recovered from any adverse effects by the day 14 observation.

Both animals made the expected body weight gains.

CONCLUSION

The notified chemical is slightly irritating to the skin.

TEST FACILITY Envigo (2017f)

B.7. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage

Vehicle None.

Remarks - Method GLP compliant.
No protocol deviations.

Negative control: 0.9% w/v Sodium chloride.
Positive control: Ethanol

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	1.67 (± 0.58)	0.020 (± 0.001)	1.96 (± 0.57)
*Test substance**	6.3 (± 1.73)	0.09 (± 0.01)	7.58 (± 1.84)
*Positive control**	29.63 (± 4.73)	1.06 (± 0.15)	45.49 (± 5.49)

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

Remarks - Results Positive and negative controls performed as expected.

The IVIS for the test substance was 7.6. As this value was between 3 and 55, no prediction regarding the eye irritation potential of the notified chemical can be made.

CONCLUSION No prediction can be made on the eye irritation potential of the notified chemical based on the conditions of the test.

TEST FACILITY Envigo (2016d)

B.8. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 492 Reconstructed Human Cornea-like Epithelium (RhCE) Test Method for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation of Serious Eye Damage.
MatTek Corporation Protocol : EpiOcular™ Eye Irritation Test for the Prediction of Acute Ocular Irritation of Chemicals for use with the MatTek Corporation's Reconstructed Human EpiOcular™ Model

Vehicle None.

Remarks - Method GLP compliant.
No protocol deviations.

Negative control: Deionised water.
Positive control: Methyl acetate.

RESULTS

Test material	*Mean OD_{570} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.417	100
Test substance	0.493	34.8
Positive control	0.409	28.9

OD = optical density

Remarks - Results The positive and negative controls performed as expected.

CONCLUSION The notified chemical was considered to be irritating to the eye under the conditions of the test.

TEST FACILITY Envigo (2017g)

B.9. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 442C *In Chemico* Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA) (2015)

Vehicle Dimethylsulfoxide (DMSO):acetonitrile

Remarks - Method The test substance and controls (p-Benzoquinone and Benzoic acid) were prepared in 1:1 DMSO:acetonitrile (100 mM stock solution). Solvent reference controls were setup and used in parallel to sample preparation in order to verify the validity of the test run. 125 mM stock solutions of cysteine and lysine peptides were prepared in dimethylformamide and Peptide reaction/Storage buffer respectively. The test substance was incubated in dark at room temperature with the peptide solutions for 24 h. The ratios of test substance: peptides were 1:10 cysteine peptide and 1:50 lysine peptide. After incubation, peptide depletion was monitored by HPLC (LC/MS/MS) coupled with a UV detector (wavelength not provided).

RESULTS

Sample	*Cysteine Peptide Depletion (% ± SD)*	*Lysine Peptide Depletion (% ± SD)*
Vehicle	0.00*	0.00*
Test Substance	6.3 (± 12.5)	1.7 (± 13.1)
Control - p-Benzoquinone	98.3 (± 0.2)	97.9 (± 0.7)
Control - Benzoic Acid	-6.7 (± 5.8)	-1.1 (± 10.0)

* – normalised to 100%; SD = Standard Deviation

Remarks - Results The reactivity of the test substance with the peptides measured as depletion of peptides was less than the percentage (6.38%) required for categorization as class I sensitiser.

The positive controls and references fulfilled all quality criteria confirming the validity of the test.

CONCLUSION The test substance was not considered a Category 1 skin sensitiser.

TEST FACILITY Cyprotex (2014)

B.10. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 442d *In Vitro* Skin Sensitisation: ARE-Nrf2 Luciferase Test Method (2015)
Vehicle	Dimethylsulfoxide (DMSO)
Remarks - Method	No significant deviations from the OECD test guideline. KeratinoSens™ test method was used. A 200 mM stock solution of test substance was prepared in dimethyl sulphoxide (DMSO) and a set of twelve master solutions were prepared in DMSO from this stock solution (0.978, 1.95, 3.91, 7.81, 15.6, 31.3, 62.5, 125, 250, 500, 1000 and 2000 µM). The master solutions used in the assay were further diluted for a final dose on the plates of 1X. DMSO and cinnamic aldehyde (4, 8, 16, 32, and 64 µM) were used as negative and positive controls respectively. Three independent assays were conducted. Each assay included a set of 4 plates (3 for gene induction, 1 for cytotoxicity assessment). Maximal induction of luciferase activity was measured at 565 nm (relative light units), while maximal gene induction (cytotoxicity assessment) was measured using absorption values at 570 nm. A test substance is predicted to have sensitisation potential if: - the EC1.5 value is < 1,000 µM in at least 2 of 3 repetitions, - cellular viability was > 70% at the lowest concentration with a gene induction > 1.5, - there was an apparent overall dose response which was similar between repetitions. The mean values for cell viability and luciferase induction were provided. Individual values from the replicate experiments were not included in the report.

RESULTS

Sample	*Mean EC1.5 (µM)*	*Mean IC50 (µM)*	I_{max}
Test substance	> 2,000	100.73	1.16
Positive Control	7.83	> 64	not provided

EC1.5 - concentration for an induction of luciferase activity 50% above vehicle control
IC50 - concentration leading to 50% cell viability compared to vehicle control
I_{max} *– maximal induction*

Remarks - Results	The lowest concentration of test substance that produced gene induction above 1.5 was 100.73 µM, and the EC1.5 value was greater than 2,000 µM. The study authors reported that the test substance did not meet the criteria for categorisation as a potential sensitiser based on a mean luciferase induction level (EC1.5) of > 1,000 µM of test substance and a mean cell viability for the cells of > 70%. The positive and vehicle controls were reported to have performed as expected.
CONCLUSION	The substance was not considered a Category 1 skin sensitiser.
TEST FACILITY	IIVS (2014)

B.11. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)
Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	Acetone/olive oil 4:1
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde
Remarks - Method	GLP Compliant. No deviations from the protocol.

RESULTS

Concentration (% v/v)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	1520.74	-
10	5 F	1127.34	0.74
25	5 F	2716.68	1.79
50	5 F	3181.27	2.09
Positive Control			
25	5 F	13063.76	8.59

Remarks - Results	The animal exposed to the test substance at 100% exhibited very slight erythema on day 3. Ear thickness was also measured before after exposure and no significant changes were noted at a concentration of 50%. Positive and negative controls performed as expected. Animals in the main study did not exhibit any signs of irritation or systemic toxicity. All animals made the expected gains in body weight.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Envigo (2017h)

B.12. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (at 5% concentration)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: patches infused with 0.2 mL test substance were applied 3 times per week on Mondays, Wednesdays and Fridays for a total of 9 applications. Patches were removed after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 14 days Challenge Procedure: identical patches were applied to naïve sites. Patches remained in place for 24 h. Sites were graded at 24 h (patch removal), 48 h and 72 h post-challenge application.
Study Group	114 (89 F, 25 M); age range 19 - 68 years
Vehicle	Alcohol SD3A:DEP
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm × 3.63 cm patch.

RESULTS

Remarks - Results	101/114 subjects completed the study. Thirteen subjects discontinued the study for reasons unrelated to the application of the test substance (5/13 received no applications (2 of these subjects were replaced by 2 new subjects who completed the study), 1/13 received one application, 1/13 received two applications, 1/13 received four applications, 2/13 received six applications, 1/13 received seven applications and 2/13 did not attend the challenge phase). Of the 101 subjects who completed the study six were absent for the last induction (ninth), but completed the challenge applications. Of the 101 subjects who completed the study, none exhibited visible skin reactions during the induction or challenge phases.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2014)

B.13. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species/Strain	Rat/Crl:WI(Han)
Route of Administration	Oral – diet
Exposure Information	Total exposure days: female: 25 or 26 days Total exposure days: male: 22 days Dose regimen: 7 days per week
Vehicle	None
Remarks - Method	GLP compliant. No significant deviations from the protocol. A 14-day dose ranging study was performed to select dosage concentrations. Doses ranged from 0, 450, 1,500, 4,500 and 11,250 mg/kg diet. Animals exposed to the highest dose exhibited a reduction in food intake and body weight, and increased liver and kidney weights. Animals exposed to the next highest dose (4,500 mg/kg diet) exhibited an increase in kidney weight. Functional observation tests were performed on 5 animals/sex/group with a litter prior to sacrifice.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration* *Nominal (mg/kg diet)*		*Actual mg/kg bw/day*	*Mortality*
control	12 M, 12 F	0	-	-	0/12 M, 0/12 F
low dose	12 M, 12 F	450	Males Females	Pre- and post-mating: 28 Pre-mating: 34 Gestation: 35 Lactation: 51	0/12 M, 0/12 F
mid dose	12 M, 12 F	1500	Males Females	Pre- and post-mating: 93 Pre-mating: 115 Gestation: 115 Lactation: 177	2/12 M, 0/12 F
high dose	12 M, 12 F	4500	Males Females	Pre- and post-mating: 265 Pre-mating: 328 Gestation: 337 Lactation: 507	0/12 M, 0/12 F

Mortality and Time to Death

There were two unscheduled deaths during the study period (males, mid-dose group). Neither death was considered related to exposure to the test substance by the study authors. The animal that was found dead on Day 4 of the pre-mating period exhibited adverse changes in the thoracic cavity, abdominal cavity, urinary bladder, kidneys, prostate, seminal vesicles, adrenals, intestines, lymphoid organs, inguinal regions and thymus which the study authors considered to be subsequent effects due to necrosis and inflammation around the urethra. The second unscheduled death occurred while the animal was under anaesthesia during blood collection. Changes in the kidney (minimal basophilic tubules and a minimal increase of proteinaceous droplets in the tubuli), liver (mild congestion, mild centrilobular hypertrophy and mild focal mononuclear cell inflammation), thymus (microhaemorrhages) and thyroid (ectopic thymus).

No similar findings were observed in any other rats exposed to the test substance and the study authors considered the deaths unrelated to treatment.

Both males were replaced by other males of the same group (mid-dose) for the purposes of the mating period.

Clinical Observations

Encrustations and/or wounds were observed pre-mating (1/12 males in the control group; 1/12 males, 3/12 females in the low-dose group; 3/12 males, 1/12 females in the mid-dose group and 1/12 males and 1/12 females in the high-dose group), post mating (1/12 males in the low-, mid- and high-dose groups), and lactation (1/10 females in the control groups), sparsely haired areas were observed during gestation (1/12 females in the control, mid-, and high-dose groups and 3/12 females in the mid-dose group) and lactation (1/11 females in the low- and high-dose groups), and piloerection was observed during lactation (1/11 females in the low- and high-dose groups). No other adverse effects were observed and the study authors considered these effects to be unrelated to the test item. No adverse effects in neurobehaviour were indicated in animals exposed to the test item.

All animals made the expected body weight gains. There was no significant difference in food consumption, although animals in the high-dose group exhibited lower food consumption over the study period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No toxicologically relevant effects were observed on haematology or clinical biochemistry. Females in the high-dose group exhibited statistically significant increases in total white blood cell count, absolute lymphocyte count and a decrease in eosinophil percentage (also observed in low-dose females), cholesterol and phospholipids, gamma glutamyl transferase activity (GGT) and calcium concentration (also observed in low-dose females). These changes were not considered to be related to exposure to the test item by the study authors as the values were within the range of historical control data, were not supported by other clinical data (there was no correlating change in absolute eosinophil counts, and the increase in calcium concentration may have been pronounced due to the relatively low levels observed in the control group), were observed in one sex only, and no dose-response relationship was observed. While aspartate aminotransferase activity (ASAT) was statistically significantly decreased in males of the mid- and high-dose group, the study author did not consider this to be a toxic effect as a result of exposure to the test item because an increase in ASAT levels is considered to represent a toxic effect, not a decrease.

Effects in Organs

Of the animals that survived to scheduled necropsy, absolute and relative liver weights were statistically significantly increased (~21%) in males in the high-dose group. No other significant weight changes, macroscopic or histopathological changes or other changes were observed that the study authors considered to be inconsistent with the background pathology of rats of this strain and age. No significant increase in kidney weight was observed.

Effects on Dams

No significant effects on the fertility, pre-coital time, reproductive performance or gestation time were observed in animals exposed to the test item. The study authors did not consider the two litters with stillborn pups (one in the control group and one in the high-dose group) to not be treatment related as this level of stillbirth is considered to be normal for rats of this strain and age.

Effects on Foetus

No toxicologically relevant effects were observed in the number of pups born, the sex ratio, live birth index or viability index, or mean pup weight. No exposure related signs were observed in pups during the lactation period and no adverse effects were observed during macroscopic examination.

Remarks – Results

No toxicologically relevant effects in relation to exposure to the test substance were observed. Increases in the total white blood cell count, absolute lymphocyte count and cholesterol and phospholipid concentrations in high-dose females were statistically significant, but were not considered to be adverse by the study authors as the change was only observed in females and the levels were within the range of historical control data.

Males in the high-dose group exhibited increased liver weight. This increase was consistent with that observed in the range finding study (at a dose of 11,250 mg/kg diet) and as such the study authors considered the increase to be related to exposure to the test item. No correlating adverse clinical or histopathological changes were observed and the study authors considered the increase in liver weight to be an adaptive response rather than an adverse reaction following exposure ot the test item.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) for parental and reproductive and developmental toxicity was established as > 328 mg/kg bw/day for females and > 265 mg/kg bw/day for males in this study, based on an absence of toxicity at the maximum dose tested.

TEST FACILITY	Triskelion (2016)

B.14. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure and treat and plate test
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Concentration Range in Test 1	*S. typhimurium* strains a) With metabolic activation: 4.7 – 150 µg/plate b) Without metabolic activation: 4.7 – 150 µg/plate *E.coli* strain a) With metabolic activation: 313 –5,000 µg/plate b) Without metabolic activation: 313 –5,000 µg/plate
Test 2	*S. typhimurium* strains a) With metabolic activation: 1.9 – 150 µg/plate b) Without metabolic activation: 1.9 - 150 µg/plate *E.coli* strain a) With metabolic activation: 62 –5,000 µg/plate b) Without metabolic activation: 62 –5,000 µg/plate
Vehicle	Dimethylsulfoxide
Remarks - Method	No deviations from the study plan. Test 1 and 2 were each run twice. Under the conditions of test 1, the first test examined all strains against a concentration range of 62 – 5,000 µg/plate in the presence and absence of metabolic activation. As less than three non-toxic concentrations were tested, this test was considered as a dose range finding test and repeated (Test 1). Under the conditions of test 2, the first test was performed using the treat and plate method, examining *S. typhimurium* strains at a concentration range of 11 – 900 µg/plate in the presence and absence of metabolic activation. As less than three non-toxic concentrations were tested, this test was repeated (Test 2) and the plate incorporation method used as this was considered more appropriate as it allowed for exposure of the bacteria to higher concentrations of the test substance..

Plate incorporation tests: Positive controls: without metabolic activation – sodium azide (TA1535, TA100), 9-aminoacridine (TA1537), 2-nitrofluorene (TA98), and N-ethyl-N-nitrosourea (WP2uvrA); with metabolic activation – 2-aminoanthracene (TA1535, TA98, TA100, WP2 uvrA) and benzo(a)pyrene (TA1537).

Treat and plate test (test 2): Positive controls: without metabolic activation – 1-methyl-3-nitro-1-nitrosoguanidine (TA1535, TA100, WP2 uvrA), 9-aminoacridine (TA1537), and 2-nitrofluorene (TA98); with metabolic activation – 2-aminoanthracene.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 556	≥ 150	> 5,000	negative
Test 2		≥ 150	> 5,000	negative
Present				
Test 1	≥ 556	> 150	> 5,000	negative
Test 2		≥ 150	> 5,000	negative

Remarks - Results

A reduction in the bacterial lawn was noted in Test 1 at ≥ 150 µg/plate (TA1537) in the absence of metabolic activation, but reduction was not > 50% in the presence of metabolic activation. Under the conditions of Test 2, a reduction in the bacterial lawn was noted at ≥ 150 µg/plate (TA1537) in the presence and absence of metabolic activation A reduction in the background lawn was observed for *E.coli* strains at ≥ 5,000 µg/plate in the presence and absence of metabolic activation.

No significant dose-related increase in the number of revertants, in the presence or absence of metabolic activation was observed.

Positive and negative controls performed as expected confirming the validity of S9-mix and the test system.

CONCLUSION

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

TEST FACILITY

TNO (2014a)

B.15. Genotoxicity – *in vitro*

TEST SUBSTANCE

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test

Species/Strain: Human

Cell Type/Cell Line: Lymphocytes

Metabolic Activation System: S9 fraction from Aroclor 1254 induced rat liver

Vehicle: Dimethylsulfoxide

Remarks - Method: GLP compliant.
No deviations from the protocol.
Positive controls: without metabolic activation – mitomycin C; with metabolic activation – cyclophosphamide.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			

Test 1	3.6, 7.2*, 14, 29*, 58*, 115, 230, 460, 920, 1842	4	24
Test 2	2, 4, 8, 16, 21*, 29, 38*, 51*, 68, 90, 120	24	24
Present			
Test 1	3.6, 7.2*, 14*, 29, 58*, 115, 230, 460, 920, 1842	4	24
Test 2	8, 16, 21, 29*, 38, 51*, 68, 90*, 120, 160	4	24

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 51	≥ 58	> 1842	none
Test 2		≥ 51	> 120	none
Present				
Test 1	≥ 58	≥ 58	> 1842	none
Test 2		≥ 90	> 160	none

Remarks - Results

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

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

TNO (2014b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test
Inoculum	Activated sludge
Exposure Period	28 day
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Maximum Inorganic Carbon Production (ThIC)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
2	0	2	63
6	0	6	76
8	0	8	84
10	0	10	74
14	0	14	81
16	0	16	86
21	0	21	79
28	1	28	81

Remarks - Results	All validity criteria of the test guideline were satisfied. The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 14 days (81%). Therefore, the tests indicate the suitability of the inoculums. The toxicity test showed no toxic effects of the test substance to the micro-organisms at the test concentration of 25.6 mg/L. The degree of degradation of the test substance after 28 days was 1%.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Envigo (2017i)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE

METHOD	OECD TG 203 Fish, Acute Toxicity Test - Semi-static aquatic system
Species	*Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	70 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography coupled with Flame Ionization Detector
Remarks – Method	The fish were exposed to the control and test solutions for a period of 96 hours with renewal of the test solution and controls every 24 hours.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative mortality*			
Nominal	*Actual (geometric mean value)*		*24 h*	*48 h*	*72 h*	*96 h*
Control	0	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
0.9	0.63	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1.4	0.99	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2.2	1.65	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3.4	2.98	10	8 (80%)	9 (90%)	9 (90%)	9 (90%)
5.2	4.49	10	10 (100%)	10 (100%)	10 (100%)	10 (100%)

LC50	2.466 mg/L at 96 hours
NOEC (or LOEC)	Not reported
Remarks – Results	All validity criteria of the test guideline were satisfied, except there was evidence that the test substance was not satisfactorily maintained. Therefore, results were based on measured concentrations. The 96 h LC50 for fish was determined to be 2.466 mg/L (the confidence limits were not reported), based on mean measured concentrations.

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

TEST FACILITY SXZD (2014)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static conditions and EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia -

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	Not measured
Analytical Monitoring	Gas Chromatography coupled with Flame Ionization Detector
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual (geometric mean measured)*		*24 h*	*48 h*
Control	0	20	0 (0%)	0 (0%)
1.0	0.40	20	0 (0%)	0 (0%)
3.2	1.3	20	0 (0%)	0 (0%)
10	4.1	20	2 (10%)	2 (10%)
32	13	20	1 (10%)	16 (80%)
100	38	20	20 (100%)	20 (100%)

EC50	1.2 mg/L at 48 hours (95% CI 1.1 – 1.3 mg/L)
NOEC (or LOEC)	0.56 mg/L at 48 hours
Remarks - Results	All validity criteria of the test guideline were satisfied. The system was static - test preparations were not renewed and conditions of the test were maintained. The 48 h EC50 and NOEC for Daphnia were determined to be 1.2 mg/L (95% CI 1.1 – 1.3 mg/L) and 0.56 mg/L, respectively, based on mean measured test concentrations.

CONCLUSION The notified chemical is considered to be toxic to aquatic invertebrates.

TEST FACILITY Envigo (2017j)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test and EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0.5 - 50 mg/L Actual: 0.41 - 43 mg/L (at 0 hours) and 0.40 to 42 mg/L (at 72 hours)
Auxiliary Solvent	None
Water Hardness	Not measured
Analytical Monitoring	Gas Chromatography coupled with Flame Ionization Detector
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Biomass (yield)		*Growth*	
EyC50 *mg/L at 72 h*	*NOEC* *mg/L*	*ErC50* *mg/L at 72 h*	*<Elemental value>* *mg/L*
4.1 (4.0 – 4.2)	1.3	9.3 (7.7 – 11.3)	1.3

Remarks - Results	All validity criteria of the test guideline were satisfied. There was no significant decline in the measured concentrations at 72 hours indicating that the test item was stable under test conditions. The 72 h ErC50 and NOEC for algae were determined to be 9.3 mg/L (95% CI 7.7 – 11.3 mg/L) and 1.3 mg/L, respectively, based on mean measured concentrations.
CONCLUSION	The notified chemical is considered to be harmful to algae.
TEST FACILITY	Envigo (2017k)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test and EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 10 – 1,000 mg/L Actual: not measured
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The reference item (3,5-dichlorophenol) gave a 3-Hour EC50 value of 6.5 mg/L, 95% confidence limits 4.9 to 8.6 mg/L.
RESULTS	
3 h IC50	520 mg/L
NOEC	100 mg/L
Remarks – Results	All validity criteria of the test guideline were satisfied. The 3 h IC50 and NOEC for were determined to be 520 mg/L (CI not determined) and 100 mg/L, respectively, based on nominal concentrations.
CONCLUSION	No toxic effects of the test substance on microbial activity at the test concentrations at least an order of magnitude higher than the test

concentration used for the biodegradation test.

TEST FACILITY	Envigo (2016e)

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