File No: LTD/1992

October 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

2(3*H*)-Furanone, 5-hexyldihydro-4-methyl-

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/1992	Symrise Pty Ltd	2(3*H*)-Furanone, 5-hexyldihydro-4-methyl-	Yes	< 1 tonne per annum	Fragrance ingredient

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*
Skin Corrosion/Irritation (Category 2)	H315 – Causes skin 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:
  - Skin corrosion/irritation (Category 2): H315 – Causes skin 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
  - Good general ventilation, including local exhaust ventilation if 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

- 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

  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;
- the concentration of the notified chemical exceeds or intended to exceed 4.8% in end-use products

or

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

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

Safety Data Sheet
The SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Symrise Pty Ltd (ABN: 67 000 880 946)
168 South Creek Road
DEE WHY NSW 2099

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)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA (2004), EU (2016) Korea (2011)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Aprifloren®

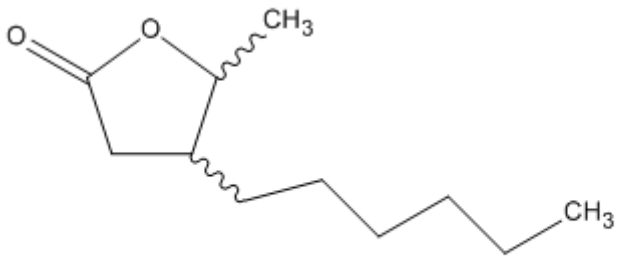
CAS NUMBER
67663-01-8

CHEMICAL NAME
2(3*H*)-Furanone, 5-hexyldihydro-4-methyl-

OTHER NAME(S)
5-Hexyldihydro-4-methylfuran-2(3H)-one.
5-Hexyldihydro-4-methyl-2(3H)-furanone
PEACHOLIDE

MOLECULAR FORMULA
$C_{11}H_{20}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
184.28 Da

ANALYTICAL DATA
Reference NMR, GC-MS, IR, GC, GPC, UV-Vis and optical activity spectra were provided.

Based on the analytical results, the notified chemical is a racemic mixture, containing enantiomers of trans-5-hexyl-4-methyl-tetrahydrofuran-2-one at approximately 57% and cis-5-hexyl-4-methyl-tetrahydrofuran-2-one at approximately 40%.

3. COMPOSITION

DEGREE OF PURITY
> 95%

IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None identified

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless to yellowish clear liquid

Property	Value	Data Source/Justification
Melting Point /Freezing Point	< -100 °C	Measured
Boiling Point	287-289 °C at 101.3 kPa	Measured
Density	938.7 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.45 × 10^{-3} kPa at 25 °C	Measured
Water Solubility	0.24 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities, however, the notified chemical is not expected to be hydrolysed significantly under normal environmental conditions of pH 4 to 9.
Partition Coefficient (n-octanol/water)	log Pow = 3.15 at 25 °C	Measured
Adsorption/Desorption	log Koc = 2.9 at 23.3 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	141 °C at 102.35 kPa	Measured
Flammability limits	Not determined	-
Autoignition Temperature	320 °C at 99.79 kPa	Measured
Explosive Properties	Not determined	This chemical does not contain any functional groups commonly associated with explosive properties.
Oxidising Properties	Not determined	Not expected to be oxidising, based on the structure.

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia either in its neat form, as a component of fragrance preparations (at concentrations ≤ 32%) or as a component of end-use products (at concentrations ≤ 4.8%).

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

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

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
Symrise Pty Ltd

TRANSPORTATION AND PACKAGING
When imported in its neat form, the notified chemical will be imported in lacquered steel flat cans, typically 30 L in size. The notified chemical will also be imported into Australia as a component of fragrance preparations (at concentrations ≤ 32%) in 30 L or 216 L lacquered metal drums or in 30 L plastic canisters, and transported by road to the notifier's facility. The imported end-use products (containing the notified chemical at ≤ 4.8% concentration) will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in a variety of cosmetic and household products (at maximum usage concentrations of 4.8% in fine fragrances, 0.21% in other cosmetic products and 0.2% in household products). The typical concentrations used in many product types will be lower than the maximum concentrations intended: 0.01% in fine fragrances, 0.002% in other cosmetic products, and 0.0002% in household cleaning products.

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

Reformulation
At the customer facilities, the notified chemical will be formulated into either a fragrance formula or 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 (≤ 0.2% concentration) may be used by consumers and professional workers (such as cleaners). The products may be used in either closed systems or open manual processes including rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at up to 4.8% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and Warehouse workers	-	-
Blending, packaging and maintenance workers	4	2
Quality Control workers	0.5	2
Beauty care and Cleaning workers	1–8	200

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemical in its neat form, as a component of fragrance preparations (at concentrations ≤ 32%) or as a component of end-use products (at concentrations ≤ 4.8%) only in the event of accidental rupture of the drum containers.

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

Formulation of end products

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

Beauty care and cleaning professionals

Exposure to the notified chemical in end-use products (at ≤ 4.8% concentration and usually at < 0.21%) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hairdressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use PPE to minimise repeated exposure, but the use of PPE 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 ≤ 4.8% 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.

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

inhaled is 50%, with the remainder ending up, as intended, on the hair. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (dermal exposure)

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.21	1	0.2566
Face cream	1,540	0.21	1	0.0505
Hand cream	2,160	0.21	1	0.0709
Fine fragrances	750	4.8	1	0.5625
Deodorant (non-spray)	1,500	0.21	1	0.0492
Shampoo	10,460	0.21	0.01	0.0034
Conditioner	3,920	0.21	0.01	0.0013
Shower gel	18,670	0.21	0.01	0.0061
Hand wash soap	20,000	0.21	0.01	0.0066
Hair styling products	4,000	0.21	0.1	0.0131
Total				**1.0203**

C = concentration of the notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.2	0.95	10	0.0068
Fabric softener	90	0.2	0.95	10	0.0027
Total					**0.0095**

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Usage (g/cm^3)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.2	1,980	0.01	0.01	0.007	0.000062
Dishwashing liquid	3	0.2	1,980	0.009	0.01	0.03	0.000501
All-purpose cleaner	1	0.2	1,980	1	0.01	0.007	0.004331
Total							**0.004894**

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness on skin × Time Scale Factor × DA/ BW

Aerosol products (Inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.21	20	1	20	50	1	10	0.0068

Daily systemic exposure = [(Amount × C × Inhalation Rate × Fraction Inhaled × 0.1) / BW × 1440)] × [Exposure Duration (Zone 1)/Volume (Zone 1) + Exposure Duration (Zone 2)/Volume (Zone 2)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 1.041 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners).

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,500 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 5,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5.27 mg/L/4 hour; low toxicity
Skin irritation (*in vitro*) Skin Corrosion - Human Skin Model Test (EpiDerm)	non-corrosive
Skin irritation (in vitro) Skin Irritation – Reconstructed Human Epidermis Model Test (EpiDerm)	irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation – adjuvant test (20%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemical were submitted. Given the low molecular weight (184.28 Da) of the notified chemical and the log Kow of 3.15, absorption across biological membranes may occur.

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

Irritation
The notified chemical is irritating to the skin but not corrosive, based on the results of *in vitro* skin irritation and corrosion studies conducted using a reconstructed human epidermis model. On the basis of these studies, the notified chemical is considered a Cat 2 skin irritant according to the GHS criteria.

Based on the results of an eye irritation study in rabbits, the notified chemical is considered not irritating to the eyes.

No information was available on the potential for respiratory irritation of the notified chemical. Acute inhalation toxicity in rats reported clear nasal discharge following exposure to aerosol of the notified chemical at 5.27 mg/L for 4 hours.

Sensitisation
The notified chemical was not found to be skin sensitising when tested up to 20% concentration in a guinea pig maximisation study using the Magnusson-Kligman method.

Repeated dose toxicity
A No Observed Adverse Effect Level (NOAEL) of 1,000 mg/kg bw/day (the highest dose tested) was established for the notified chemical by the study authors in a 28-day repeated dose oral gavage toxicity test in rats. There were increased platelet counts in low dose females and other effects in mid and high dose group animals but these were considered not treatment related by study authors. Mean absolute liver weight and relative liver weight increased in mid and high dose group animals but without macroscopic or microscopic changes.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation assay and was not considered to be genotoxic in an *in vitro* mammalian chromosome aberration test.

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

Hazard classification	*Hazard statement*
Skin Corrosion/Irritation (Category 2)	H315 – Causes skin irritation

6.3. Human Health Risk Characterisation
The notified chemical is a skin irritant. The potential for respiratory irritation cannot be ruled out.

6.3.1. Occupational Health and Safety
Reformulation
Transport, storage and reformulation workers may have dermal contact with the notified chemical at up to 100% concentration. Accidental ocular exposure is also possible. At 100% concentration and as part of fragrance oils at up to 32% there is a potential for irritation effects. Safe work practices when handling the notified chemical during reformulation processes and use of PPE including impervious gloves and coveralls would limit exposure and risk.

Provided that the above mentioned control measures and PPE are employed, the risk to the health of workers during the handling of the notified chemical at up to 100% concentration is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical, in conditions similar to public use. Cleaners may have exposure to concentrations up to 0.2% in products, and beauty care professionals would generally have exposure to similar concentrations, or to up to 4.8% if applying fine fragrances. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experience by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health
Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products (containing the notified chemical at ≤ 4.8% in individual products). The main route of exposure is expected to be dermal with some potential for inhalation and for accidental ocular or oral exposure.

Local effects
The notified chemical is irritating to the skin. However, given the relatively low proposed use concentration in end use products (≤ 4.8%), irritation effects are expected to be greatly reduced.

Systemic effects
The potential systemic exposure to the public from the use of the notified chemical in cosmetics and household products was estimated to be 1.041 mg/kg bw/day (see Section 6.1.2) using the highest concentration of use for the product types. Using a NOAEL of 1,000 mg/kg bw/day, which was established in a 28-day repeat dose oral toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 960. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with the proposed use of the notified chemical at ≤ 4.8% in fine fragrances, ≤ 0.21% in other cosmetic products and ≤ 0.2% in household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported neat or as a component of fragrance formulations, for reformulation into finished cosmetic formulations and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. It is estimated by the notifier that a maximum of 0.1% of the import volume of the notified chemical (or up to 1 kg) may be released from accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with absorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical to the environment from this process is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail sale and use. Wastes containing the notified chemical generated during reformulation include equipment wash water, residues from empty import containers and spilt materials. Wastes containing the notified chemical generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. Wash waters are expected to be recycled or released to on-site waste water treatment processes, or sewers in a worst case scenario. Empty import containers and residues are expected to be recycled or disposed of through licensed waste management services.

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
It is estimated by the notifier that a maximum of 1% of the import volume of the notified chemical (or up to 10 kg), may remain in end-use containers once the consumer products are used up. 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 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. Based on the results of a ready biodegradability study, the notified chemical is considered readily biodegradable (82% in 28 days). For details of the environmental fate study, please refer to Appendix C. Based on its adsorption coefficient (log Koc = 2.9) it is expected to have low mobility in soil. The notified chemical is not expected to bioaccumulate based on its partition coefficient (log Kow = 3.15) and ready biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile from water (vapour pressure = 1.45×10^{-3} kPa at 25 °C) and may slowly volatilise to air during sewage treatment. The half-life of the notified chemical in air is calculated to be < 1 h, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when sewage sludge is used for soil remediation. The notified chemical may also be applied to land when disposed of to landfill as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually 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 0.56 µg/L may potentially result in a soil concentration of approximately 3.74 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 18.73 µg/kg and 37.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 11.5 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 2.98 mg/L	Toxic to aquatic invertebrates
Algal Toxicity	48 h EC50 = 8.52 mg/L	Toxic to algae
Inhibition of Bacterial Respiration	3 h IC50 32 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints, the notified chemical is considered to be toxic to aquatic life. 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; Harmful to aquatic life'. Based on the acute toxicity, ready biodegradability and low potential for bioaccumulation, the notified chemical is not formally classified under the GHS for chronic toxicity.

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for Daphnia. A safety factor of 100 was used given acute endpoint for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Daphnia, 48 h)	2.98	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	29.8	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.56	29.8	**0.018**
Q – Ocean	0.056	29.8	**0.0018**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. The notified chemical is readily biodegradable, and is expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -100 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Differential scanning calorimetry method was used.
Test Facility	Consilab (2015a)

Boiling Point 287-289 °C at 101.3 kPa

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

Density 938.7 kg/m^3 at 20 ± 0.01 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	A calibrated oscillating densitometer was used.
Test Facility	Consilab (2015b)

Vapour Pressure 9.6×10^{-4} kPa at 20 °C
1.45×10^{-3} kPa at 25 °C
9.4×10^{-3} kPa at 50 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Dynamic method: vapour-liquid equilibrium was used. Thermal stability was confirmed by DSC.
Test Facility	Consilab (2015c)

Water Solubility 0.24 g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Modified Flask Method
Test Facility	Noack Laboratorium (2015a)

Partition Coefficient (n-octanol/water) log Pow = 3.15.at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water)..
Remarks	GC-MS Method
Test Facility	Noack Laboratorium (2015b)

Adsorption/Desorption – screening test log K_{oc} = 2.9 at 23.3 °C

Method	OECD TG 121 Adsorption - Desorption Using HPLC Method
Remarks	HPLC method
Test Facility	Noack Laboratorium (2015c)

Flash Point 141.0 °C at 102.35 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	A closed cup method was used. The main study was preceded by a preliminary test.
Test Facility	Consilab (2015d)

Autoignition Temperature 320 °C at 99.79 kPa

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases) DIN 51794 (2003)
Remarks	Method DIN 51794 was used with both semi-automated and fully automated apparatuses. The approximate ignition temperature was determined in a preliminary test.
Test Facility	Consilab (2015e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (1996)
Species/Strain	Rat/Sprague-Dawley
Vehicle	None
Remarks - Method	No protocol deviations

RESULTS

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

LD50	> 2,500 mg/kg bw
Signs of Toxicity	Signs of systemic toxicity noted during the day of dosing were hunched posture, lethargy and ataxia. Hunched posture was noted in all females one day after dosing and the effects disappeared two days after dosing. Males appeared normal one day after dosing.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	All animals had expected in the bodyweight during the study.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	SafePharm Laboratories (2001)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity (1987) – Limit Test
Species/Strain	Rat/Sprague-Dawley
Vehicle	None
Type of dressing	Occlusive.
Remarks - Method	A control group was included.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	0	0/10
2	5 per sex	5,000	0/10

LD50	> 5,000 mg/kg bw
Signs of Toxicity – Local/Systemic	No clinical abnormalities were noted.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	The body weights between the control and test group were comparable.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	Biotoxtech (2015a)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity – Limit Test (2009)
Species/Strain	Rat/Wistar
Vehicle	None
Method of Exposure	Oro-nasal
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	1.40 ± 1.21 μm
Remarks - Method	An on line particle size analyser (Galai particle size analyser) was used instead a Cascade Impacter. The value for geometric standard deviation (GSD) for the test substance was 2.22, which was within the recommended range of 1.5-3.0. The GSD was > 1.2, which indicated that the aerosol was a polydisperse.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <mg/L>*		*Mortality*
		Nominal	*Actual*	
1	3 per sex	7.15 ± 0.17	5.27 ± 0.32	0/6

LC50	> 5.27 mg/L/4hours
Signs of Toxicity	Clinical signs such as clear nasal discharge, slight tremors, slight/moderate salivation, hypoactivity, ataxia and slight piloerection were observed in treated rats. These effects had all disappeared by day 5.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	The body weights of all animals decreased on day 2. The male rats gained weight from day 4. The body weight for all female rats decreased on day 4, increased on day 8 for two females and decreased for one female. All rats gained weight by day 15.

CONCLUSION	The notified chemical is of low acute toxicity via inhalation.
TEST FACILITY	Advinus (2015)

B.4. Irritation – skin (*in vitro*)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test (2014) EC Council Regulation No 440/2008 B.40. *In vitro* Skin Corrosion – Transcutaneous Electrical Resistance Test
Vehicle	None
Remarks - Method	The EpiDerm test system was used. The negative control was deionised water and the positive control was 8.0 N potassium hydroxide. A minor deviation to the protocol in the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) pre-test was not expected to affect the validity of the study.

RESULTS

Exposure of 3 minutes

Test material	*Mean OD_{570} of triplicate tissues*	*Coefficient of Variation*	*Relative mean Viability (%)*
Negative control	1.575	0.1	100.0*

Test substance	1.829	2.9	116.1
Positive control	0.139	7.1	8.8

Exposure of 60 minutes

Test material	*Mean OD_{570} of triplicate tissues*	*Coefficient of Variation*	*Relative mean Viability (%)*
Negative control	1.607	5.7	100.0*
Test substance	1.871	9.3	116.5
Positive control	0.041	13.3	2.5

OD = optical density
*The mean % viability of the negative control tissue is set at 100%.

Remarks - Results

Results for the test substance were similar to the results of the negative control at both exposure durations.

The MTT solution containing the test substance did not turn blue, confirming that the test substance did not reduce MTT. The solution containing the test substance did not become coloured, indicating that the test substance did not have the potential to cause colour interference.

The acceptance criteria for both the negative and positive controls were satisfied, and the variation between replicates was satisfactory.

As the relative mean viability of tissues exposed to the test substance was > 50% after both 3 minutes and 60 minutes exposure, the test substance did not meet the criteria for classification as a Cat.1 corrosive under the GHS.

CONCLUSION

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

TEST FACILITY

Envigo (2015)

B.5. Irritation – skin (*in vitro*)

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2013)
EC Council Regulation No 440/2008 B.46. *In vitro* Skin Irritation – Reconstructed Human Epidermis Model Test (2009)

Vehicle

None

Remarks - Method

The EpiDerm test system was used. No protocol deviations were noted. The negative control was Dulbecco's phosphate buffered saline (DPBS) and the positive control was 5% sodium lauryl sulphate (SLS).

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	1.532	100.0	9.8
Test substance	0.391	25.5	11.9
Positive control	0.104	6.8	7.9

OD = optical density; SD = standard deviation

Remarks - Results

The test substance showed reduced cell viability.

The optical pre-experiment (colour interference pre-experiment) to investigate the test substance's colour change potential in water did not lead to a change in colour. Optical evaluation of the MTT-reducing capacity of the test substance after 1 hour incubation with MTT-reagent did

not show blue colour. Based on the above, the test substance did not cause colour interference.

The criteria for acceptance of both the negative and positive controls were satisfied, as were the requirements for standard deviation between the replicates.

The test substance meets the criteria for classification as a Cat. 2 skin irritant under the GHS as the relative mean viability of the tissues treated with the test substance in this study was < 50%.

CONCLUSION	The notified chemical was irritating to the skin under the conditions of the test.
TEST FACILITY	Harlan (2015a)

B.6. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (2012)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	72 h
Remarks - Method	No protocol deviations. One animal was used in the initial test while two animals were used in confirmatory test.
RESULTS	
Remarks - Results	All scores for corneal, iridial and conjunctival effects were zero. During the observation period, no abnormal clinical signs were noted in any animal. Body weight gain was as expected.
CONCLUSION	The notified chemical is non-irritating to the eye.
TEST FACILITY	Biotoxtech (2015b)

B.7. Skin sensitisation

TEST SUBSTANCE	Notified chemical (supplied as 20% in liquid paraffin)
METHOD	OECD TG 406 Skin Sensitisation - <Magnusson and Kligman> (1992) EC Directive 96/54/EC B.6 Skin Sensitisation - <Magnusson and Kligman>
Species/Strain	Guinea pig/albino
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 20% intradermal: 1% and 5% topical: 2%, 5% and 10%
MAIN STUDY	
Number of Animals	Test Group: 10 M Control Group: 5 M
Vehicle	Liquid paraffin BP
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 2-mercaptobenzothiazole and α-hexylcinnamaldehyde.
INDUCTION PHASE	Induction Concentration: intradermal: 5% topical: 20%

Signs of Irritation	Discrete or patchy to moderate and confluent erythema was observed at the intradermal induction sites of test group animals. Discrete or patchy erythema was observed at the intradermal induction sites of control group animals. Discrete or patchy erythema was observed at the topical induction sites of test group animals. No evidence of erythema or oedema was observed at the topical induction sites of control group animals. Bleeding from the intradermal injection sites was observed in 6 test group animals and one control group animal.
CHALLENGE PHASE	
challenge	topical: 10% and 20%
Remarks - Method	No protocol deviations. Dosage concentrations were adjusted to take account of the concentration of the notified chemical as supplied.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	10%	0/10	0/10
	20%	0/10	0/10
Control Group	10%	0/5	0/5
	20%	0/5	0/5

Remarks - Results	No skin reactions were observed at the challenge sites of the test or control group animals at the 24 or 48-hour observations with challenge concentrations of 10% and 20%. The body weight gains between the control and test group animals were comparable.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.
TEST FACILITY	SafePharm Laboratories (2002)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)
Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: none
Vehicle	Corn oil
Remarks - Method	No protocol deviations. Doses were chosen on the basis of a range-finding study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	62.5	0/10

mid dose	5 per sex	250	0/10
high dose	5 per sex	1,000	0/10

Mortality and Time to Death
All animals survived the duration of the study.

Clinical Observations
Test substance related temporary changes such as salivation in all test groups and irregular respiration in the high dose group were considered temporary since it was observed temporarily or sporadically or there were no corresponding changes on salivary glands at necropsy and histopathological examination.

No clinical abnormalities in detailed examinations were noted in all test groups. For the body weights, body weight gains, food consumption, and relative food consumption, the test groups were statistically comparable with the control group. There were no differences between groups in the functional observations study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
For urinalysis, haematology and clinical chemistry, any changes in the parameters, such as statistically significant increases in platelet counts in low dose females, or reduced total bilirubin in mid and high dose males and increased total protein in high dose females, were considered not to be of toxicological significance due to small magnitude, likely due to biological variation, lack of dose-response and inconsistency in both sexes and related parameters.

Effects in Organs
A test substance related increase in the mean absolute liver weight (8.33 g/ 100 g bw) was statistically significant in high dose females. Relative liver weight increases noted in males and females in the mid and high dose groups were also statistically significant (3.40 and 3.66 g/100 g/100 g bw in males and 3.44 and 3.77 g/100 g bw in females, respectively). These effects were considered by study authors to have little toxicological significance since they were not consistently related to clinical chemistry parameters or to macroscopic or microscopic changes in the liver.

Other sporadic organ weight changes of statistical significance were not considered by study authors to be toxicologically important because of small magnitude and no associated effects in organs.

The macroscopic findings at necropsy were considered by the study authors to be incidental and not related to the test substance. Similarly, the histopathological findings (controls and high dose group only examined) were not considered to be test substance related or of toxicological significance.

Remarks – Results
The study authors considered that none of the observed effects were test substance related.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 1,000 mg/kg bw/day.

TEST FACILITY Biotoxtech (2015c)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Plate incorporation procedure (test 1) Pre incubation procedure (test 2)
Species/Strain	*Salmonella typhimurium strains*: TA1535, TA1537, TA98, TA100 *Escherichia coli strains*: WP2uvrA
Metabolic Activation System	Phenobarbital/β-Naphthoflavone induced rat liver S9
Concentration Range in Main Test	a) Test 1: 0, 3, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate b) Test 2: 0, 1, 3, 10, 33, 100, 333, 1,000 and 2,500 µg/plate
Vehicle	DMSO
Remarks - Method	Minor deviation did not affect the validity of the study. The criteria for an

increase in revertants considered to be positive was two-fold for TA 98, TA 100, and WP2uvrA, and three fold for TA 1535 and TA 1537. The preliminary test is reported as test 1.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 333	> 5,000	negative
Test 2	≥ 100	> 2,500	negative
Present			
Test 1	≥ 1,000	≥ 1,000	negative
Test 2	≥ 1,000	> 2,500	negative

Remarks - Results

No substantial increase in revertant colony numbers of any of the five tester strains was noted following treatment with the test substance at any dose level, either in the presence or absence of S9 mix. No tendency of higher mutation rates with increasing concentrations was observed in the biologically relevant range.

A high number of revertants of the TA1537 strain were seen in the untreated control in Test 2 with metabolic activation, however this is not relevant to the mutagenic potential of the test substance.

The concurrent positive controls and the other negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY

Harlan (2010)

B.10. Genotoxicity – *in vitro*

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (2014)

Cell Type/Cell Line: Human lymphocytes

Metabolic Activation System: Phenobarbital/β-Naphthoflavone induced rat liver S9

Vehicle: DMSO

Remarks - Method: Minor deviation did not affect the validity of the study.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 12.30, 21.53, 37.68, 65.94, 115.40*, 201.94*, 353.40*, 618.45, 1082.29, 1894.00	4 h	22 h
Test 2	0, 12.30, 21.53, 37.68, 65.94*, 115.40*, 201.94*, 353.40, 618.45, 1082.29, 1894.00	4 h	22 h
Present			
Test 1	0, 12.30, 21.53, 37.68, 65.94*, 115.40*, 201.94*, 353.40, 618.45, 1082.29, 1894.00	22 h	22 h
Test 2	0, 12.30, 21.53, 37.68, 65.94*, 115.40*, 201.94*, 353.40, 618.45	4 h	22 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	not reported			
Test 1		> 1894.00	> 1894.00	negative
Test 2		> 1894.00	> 1894.00	negative
Present	not reported			
Test 1		> 1894.00	> 1894.00	negative
Test 2		> 618.45	> 618.45	negative

Remarks - Results

Phase separation was observed in test 1 at ≥ 353.40 µg/mL in the absence of S9 mix and in test 1 at ≥ 201.94 µg/mL with S9 mix. In test 2 phase separation was observed in the absence of S9 mix at a concentration of ≥ 353.40 µg/mL and in the presence of S9 mix at a concentration of ≥ 201.94 µg/mL.

With the exception of the two occurrences set out below, no statistically significant or dose related increases in the number of cells carrying structural chromosomal aberrations were noted after treatment in Test 1 or 2.

In test 1 in the absence of S9 mix, a single increase in chromosome aberrations (4.2 % aberrant cells excluding gaps) above the range of the laboratory historical solvent control data (0.0 - 3.0%) was noted after treatment at 201.94 µg/mL. Since the value was not statistically significant and no dose dependency was observed, this finding was not regarded as biologically relevant.

In test 2 in the absence of S9 mix, one statistically significant increase in chromosomal aberrations (4.8% aberrant cells excluding gaps) was noted after treatment at 115.40 µg/mL. This value was above the range of the laboratory historical solvent control data (0.0 – 3.0%). Since there was no dose dependency and it was confirmed by evaluating an additional 300 cells, the effect was considered by study authors to be irrelevant.

No evidence of an increase in polyploid metaphases was noticed after treatment with the test item as compared to the control cultures. No test substance relevant influence on osmolarity or pH was shown.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the validity of the test.

CONCLUSION

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

TEST FACILITY

Harlan (2015b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sewage sludge
Exposure Period	28 Days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		Toxicity Control		Sodium benzoate	
Day	% Degradation	Day	% Degradation	Day	% Degradation
7	15	7	31	7	83
14	61	14	42	14	90
21	79	21	62	21	94
28	82	28	73	28	96

Remarks - Results

All validity criteria for the test were satisfied. The percentage degradation of the reference compound sodium benzoate, surpassed the threshold level of 60% with an average biodegradation of 72% by day 3 and 96% at the end of the 28 days, confirming the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by day 3 with a 28% degradation and had a 73% degradation by day 28, indicating that toxicity was not a factor inhibiting the biodegradability of the test substance.

The degree of degradation of the test substance after 28 days was 82%. Biodegradation of at least 60% of the ThOD was reached within the 10-day window within the 28-day period of the test. The test substance is, therefore, considered to be readily biodegradable according to the OECD (301 F) guideline.

CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Harlan (2012)

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	*Brachydanio rerio* (Zebrafish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Not reported
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality %*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	10	0	0	0	0	0
1.25	< 0.42	10	0	0	0	0	0
2.5	2.23	10	0	0	0	0	0
5	4.38	10	0	0	0	0	0
10	11.4	10	0	20	30	30	30
20	21.7	10	0	100	100	100	100

LC50	11.5 mg/L at 48 to 96 hours
NOEC (or LOEC)	Not determined
Remarks – Results	All validity criteria for the test were satisfied. A semi-static test procedure with daily test medium renewal was used. Chemical analysis of the notified chemical test medium was done at 0 and 96 h; with no chemical measurements at intermediate time points (24, 48, 72 h), despite a semi-static testing regime. As the measured mean concentrations of the notified chemical test medium deviated ± 20% from the nominal treatment concentrations, effects measures were calculated from the geometric mean of the measured concentrations. The 96 h LC_{50} for the Zebrafish was 11.5 mg/L of the notified chemical, based on measured concentrations.
CONCLUSION	The notified chemical is considered to be harmful to fish.
TEST FACILITY	Shanghai Academy of Environmental Sciences Environmental Testing Laboratory (2010)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test – Semi-static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	160 – 180 mg $CaCO_3$/L
Analytical Monitoring	GC-MS
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. The notified chemical was expected to evaporate. To reduce losses of the notified chemical test item, the study was conducted in a closed system without headspace.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
1.00	1.04	20	0	10
2.5	2.11	20	15	25
5.0	4.03	20	40	75
10	7.79	20	60	100
20	15.7	20	80	100

EC50	2.98 mg/L (95% CI: 2.50 – 3.61) at 48 hours
NOEC	1.04 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 48 h test period. The actual concentrations of the test substance were measured at the start and every 24 hours during the 48 h test period. Since the measured notified chemical test medium concentrations did not remain within ± 20 % of the nominal

concentrations, the effect values were based on the geometric mean of the notified chemical measured concentrations. The 48 h EC_{50} for *D. magna* was 2.98 mg/L (95% CI 2.50- 3.61 mg/L), based on measured concentrations of the notified chemical.

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

TEST FACILITY Noack Laboratorium (2015d)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test – Static
Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 2.048 – 80 mg/L
Actual: 1.64 – 67.8 mg/L
Auxiliary Solvent None
Water Hardness 24 mg $CaCO_3$/L
Analytical Monitoring GC-MS
Remarks – Method The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EyC50	*NOEC*	*ErC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
3.88 (95% CI: 3.79 – 3.97)	< 1.64	8.52 (95% CI: 8.07 – 8.92)	< 1.64

Remarks – Results All validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at start and end of the 72 h test period. As measured concentrations deviated ± 20% from the nominal concentrations by the end of the test, all effects values were calculated on the geometric mean of the measured concentrations. The notified chemical inhibited the growth rate of the freshwater green alga *P. subcapitata* after 72 hours with the following effect values: Growth rate ErC_{50} 8.52 (95% CI: 8.07 – 8.92) mg/L and NOEC < 1.64 mg/L.

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

TEST FACILITY Noack Laboratorium (2015e)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test
Inoculum Activated sewage sludge
Exposure Period 3 hours
Concentration Range Actual: 10 - 1000 mg/L
Remarks – Method The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. To check the activity of the test system and the test conditions a reference test was carried out with copper (II) sulphate pentahydrate at 58 - 180 mg/L as a reference item with reference toxicity determined as EC_{50} 113 mg/L, within the required range of 53 – 155 mg/L for the test. The respiration rates as Biochemical Oxygen Demand, of the control, reference and test item replicates were

	measured after a contact time of three hours, and the inhibitory effects of the test and reference item were determined in comparison to the control respiration rates.
RESULTS	
EC50	191 mg/L (95% CI: 174 – 211) at 3 hours
NOEC	32 mg/L
Remarks – Results	The notified chemical is not toxic, up to the concentration of 32 mg/L, to activated sludge of a municipal sewage treatment plant. The 3 h EC_{50} was determined to be > 100 mg/L.
CONCLUSION	The notified chemical is not considered to inhibit microbial respiration.
TEST FACILITY	Noack Laboratorium (2015f)

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