File No.: LTD/2085 and LTD/2090

May 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

LTD/2085: 1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis[1-methyl-2-[4-(1-methylethyl)phenyl]ethyl]- and LTD/2090: TrifernalO

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2085	Henkel Australia Pty Ltd	1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis[1-methyl-2-[4-(1-methylethyl)phenyl]ethyl]-	ND*	< 1 tonne per annum	Components of household laundry and cleaning products
LTD/2090		TrifernalO	ND*	< 1 tonne per annum	

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information the notified chemicals cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*, as adopted for industrial chemicals in Australia.

Human Health Risk Assessment
Under the conditions of the occupational settings described, the notified chemicals are not considered to pose an unreasonable risk to the health of workers.

When used in the proposed manner, the notified chemicals are not considered to pose an unreasonable risk to public health.

Environmental Risk Assessment
On the basis of the low hazard and reported use pattern, the notified chemicals are not expected to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

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

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

- 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 chemicals during reformulation processes:
  - Coveralls

- Impervious gloves
- Respiratory protection if inhalation exposure may occur

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

Emergency procedures

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

Disposal

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
- the final use concentration of the notified chemicals exceeds 0.1% in household laundry and cleaning products;
- the importation volume exceeds one tonne per annum for each notified chemical;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemicals has changed from a component of household laundry and cleaning products, or is likely to change significantly;
- the amount of chemicals being introduced has increased, or is likely to increase, significantly;
- the chemicals have begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemicals 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 SDSs of the notified chemicals provided by the notifier was reviewed by NICNAS. The accuracy of the information on the SDSs remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Henkel Australia Pty Ltd (ABN: 82 001 302 996)
135-141 Canterbury Road
KILSYTH VIC 3137

NOTIFICATION CATEGORY
LTD/2085: Limited-small volume: Chemical other than polymer (1 tonne or less per year)
LTD/2090: Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Chemical is being notified at the same time as a similar chemical.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details exempt from publication include: chemical name, CAS number and structural formula for LTD/2090

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are not varied.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
LTD/2085:
Europe - ECHA (2010)
Korea - 2011
USA EPA (2012)

LTD/2090: None

2. IDENTITY OF CHEMICAL

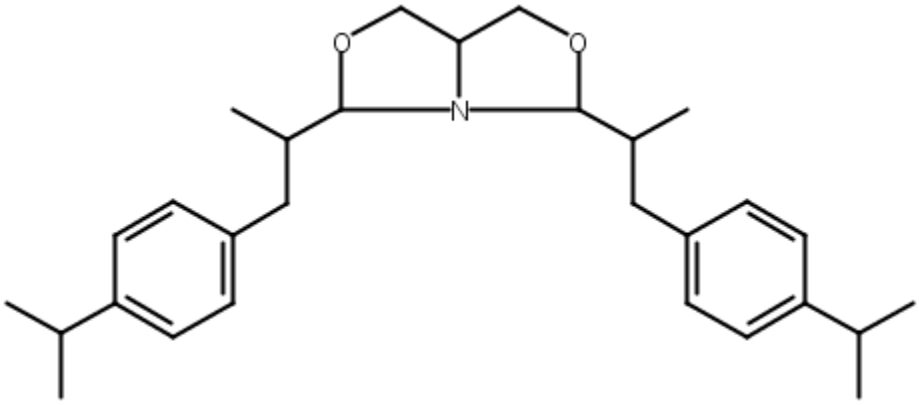
MARKETING NAME(S)
LTD/2085: Sa163
LTD/2090: TrifernalO

CAS NUMBER
LTD/2085: 1001164-15-3

CHEMICAL NAME
LTD/2085: 1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis[1-methyl-2-[4-(1-methylethyl)phenyl]ethyl]-

OTHER NAME(S)
LTD/2085: Cyclamen Oxazolidin
LTD/2090: Methyl-bis(2-arylpropyl)dihydro-heteropolycycle

STRUCTURAL FORMULA



LTD/2085

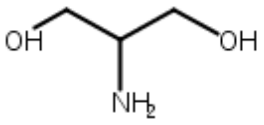
MOLECULAR FORMULA
LTD/2085: $C_{29}H_{41}NO_2$
LTD/2090: $C_{24}H_{31}NO_2$

MOLECULAR WEIGHT
LTD/2085: 435.64 g/mol
LTD/2090: 365.51 g/mol

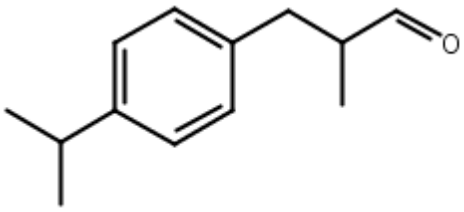
ANALYTICAL DATA
Reference NMR, IR, GC and UV spectra were provided for both chemicals.

DEGRADATION PRODUCTS

LTD/2085: 1,3-Propanediol, 2-amino- (CAS No. 534-03-2) and Benzenepropanal, α-methyl-4-(1-methylethyl)- (CAS No. 103-95-7)



CAS No. 534-03-2



CAS No. 103-95-7

3. COMPOSITION

DEGREE OF PURITY
LTD/2085: > 99%
LTD/2090: 99.7%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

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

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

LTD/2085
APPEARANCE AT 20 °C AND 101.3 kPa: cream solid

Property	*Value*	*Data Source/Justification*
Melting Point	79-85 °C (onset)	Measured
Boiling Point	322 °C at 102.1 kPa	Measured
Density	1,032 kg/m^3 at 20 °C	Measured
Vapour Pressure	≤ 3.7 × 10^{-5} kPa at 20 °C	Estimated
Water Solubility	Unstable in aqueous medium	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemical is unstable in water.
Partition Coefficient (n-octanol/water)	log Pow > 5.7 at 40 °C	Measured
Adsorption/Desorption	Not determined	The notified chemical is unstable in water.
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Not determined	Waxy solid at room temperature
Flash Point	194 °C at 101.3 kPa	Measured
Solid Flammability	Not flammable	Measured
Flammability (Contact with water)	Not flammable	Measured
Autoignition Temperature	Not detected up to 400 °C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	Measured
Pyrophoric properties	Not pyrophoric	Measured

LTD/2090
APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	*Value*	*Data Source/Justification*
Melting Point	No melting between -90 °C and 90 °C	Measured
Boiling Point	312 °C at 100.2 kPa	Measured
Density	1,059 kg/m^3 at 20 °C	Measured
Vapour Pressure	≤ 1.2 × 10^{-4} kPa at 20 °C ≤ 1.9 × 10^{-3} kPa at 50 °C	Estimated
Water Solubility	Not determined	Expected to be unstable in water
Hydrolysis as a Function of pH	Not determined	The notified chemical is expected to be unstable in water.
Partition Coefficient (n-octanol/water)	log Pow = 5.02 at 40 °C	Measured
Adsorption/Desorption	Not determined	The notified chemical is unstable in water.
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Not determined	Liquid
Flash Point	193 °C at 101.3 kPa	Measured
Flammability (Contact with Water)	Not flammable	Measured
Autoignition Temperature	395 °C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	Measured
Pyrophoric properties	Not pyrophoric	Measured

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

Reactivity
The notified chemicals are designed to hydrolyse to amine diol and aldehyde components (releasing fragrances) during their use in household laundry and cleaning products.

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

The notified chemicals have flash points greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the notified chemicals may be considered as a Class C2 combustible liquid if the chemicals have a fire point below the boiling point.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemicals will not be manufactured in Australia. The notified chemicals will be imported as a component of fragrance oils at ≤ 12% concentration (for each chemical) for local reformulation into household laundry and cleaning products, or as a component of finished products at ≤ 0.1% concentration (for each chemical).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes for each chemical	< 1	< 1	< 1	< 1	< 1

PORT OF ENTRY
Sydney and Brisbane

IDENTITY OF RECIPIENTS
Pax Australia PTY Ltd and Jalco Household & Fabric Care

TRANSPORTATION AND PACKAGING
The notified chemicals will be imported as a component of finished household laundry and cleaning products at ≤ 0.1% concentration (for each chemical) already packaged in containers suitable for retail sale, or as components of fragrance oil at ≤ 12% concentration (for each chemical) in 200 L drums and 1,000 L intermediate bulk containers (IBCs). Finished consumer products containing the notified chemicals will be transported primarily by road to retail stores in packages suitable for retail sale. Within Australia the drums and IBCs will be transported by road to industrial customers for reformulation.

USE
The notified chemicals will be used as fragrance precursors in household laundry and cleaning products at ≤ 0.1% concentration (for each chemical). The product types are laundry detergents (e.g. heavy duty detergents, light duty detergents), fabric finishers (e.g. fabric softeners, fabric conditioners), laundry additives (e.g. fragrance boosters) and hard surface and/or all-purpose cleaners. Hand and automatic dishwashing detergents are not part of the application range.

OPERATION DESCRIPTION
Reformulation
Reformulation of the fragrance oil containing the notified chemical at ≤ 12% concentration (for each chemical) into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end use products into containers of various sizes.

End-use
End use products containing the notified chemicals at ≤ 0.1% concentration (for each chemical) will be used by consumers and professional cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed. The notified chemicals will act as fragrance precursors.

They are expected to hydrolyse during end use and the degradation products may be deposited on fabrics or other surfaces.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	None	Incidental
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	1
Quality control	1	2
Packaging	4	2
Professional end-use	8	365

EXPOSURE DETAILS

Transport and storage

Transport, storage and warehouse workers may come into contact with the notified chemicals at ≤ 12% concentration (for each chemical) in fragrance oils, or at ≤ 0.1% concentration (for each chemical) in finished consumer products. However this would occur only in the unlikely event of accidental rupture of containers.

Reformulation

During reformulation dermal, ocular and perhaps inhalation exposure of workers to the notified chemicals at ≤ 12% concentration (for each chemical) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier advised that it is expected that exposure will be minimised through the use of mechanical ventilation and/or enclosed systems, and workers wearing personal protective equipment (PPE) such as protective clothing, eye protection, impervious gloves and respiratory protection, if inhalation exposure may occur.

End use

Exposure to the notified chemicals in end use products at ≤ 0.1% concentration (for each chemical) may occur in professions where the services provided involve the use of household cleaning products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible. Professional cleaners may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the products containing the notified chemicals.

6.1.2. Public Exposure

There will be repeated exposure of the public to the notified chemicals at ≤ 0.1% concentration (for each chemical) through the use of household laundry and cleaning products. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray. The public may also be exposed to degradation products of the notified chemicals, which are expected to be released during end use and may deposit on fabrics or other surfaces.

6.2. Human Health Effects Assessment

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

Endpoint	***Test Substance – Notified Chemical***	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LTD/2085	LD50 > 2,000 mg/kg bw; low toxicity
Acute oral toxicity – rat	LTD/2090	LD50 > 2,000 mg/kg bw; low toxicity

Endpoint	*Test Substance – Notified Chemical*	*Result and Assessment Conclusion*
Skin irritation – *in vitro* reconstructed human epidermis test method	LTD/2085	non-irritating
Skin irritation – *in vitro* human skin model test (EpiDerm™)	LTD/2090	non-irritating
Eye irritation – *in vitro* Hen's Egg Test - Chorioallantoic Membrane (HET-CAM test)	LTD/2085	non-irritating
Skin sensitisation – mouse local lymph node assay	LTD/2085	no evidence of sensitisation up to 25% concentration
Skin sensitisation – *in chemico DPRA test*	LTD/2090	inconclusive
Skin sensitisation – *in vitro* ARE-Nrf2 luciferase test	LTD/2090	positive
Skin sensitisation – *in vitro* human cell line activation test (h-CLAT)	LTD/2090	negative
Mutagenicity – bacterial reverse mutation	LTD/2085	non mutagenic
Mutagenicity – bacterial reverse mutation	LTD/2090	non mutagenic

Toxicokinetics
No data on toxicokinetics for the notified chemicals were provided. Chemicals with molecular weights below 100 g/mol are favourable for dermal absorption and molecular weights above 500 g/mol do not favour dermal absorption (ECHA, 2017). Based on the low molecular weight (100-500 g/mol) of the notified chemicals, absorption across biological membranes may occur. Because of their high lipophilicity (log Pow > 5), percutaneous absorption may be limited.

Acute Toxicity
The notified chemicals were of low acute oral toxicity when tested in rats.

Irritation
According to the results of *in vitro* assays conducted to test the skin irritation potential of the two notified chemicals, neither are considered to be irritating to the skin according to the test guidelines used and therefore, not classified as skin irritants.

In an *in vitro* Hen's Egg Test - Chorioallantoic Membrane (HET-CAM) study (non guideline study) conducted on one of the notified chemicals (LTD/2085), the notified chemical is not considered to be irritating to the eyes.

Sensitisation
One of the notified chemicals (LTD/2085) was not a skin sensitiser up to the 25% concentration tested in a mouse local lymph node assay (LLNA).

One *in chemico* and two *in vitro* cell based assays were conducted to evaluate the skin sensitisation potential of the notified chemical LTD/2090. 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, 2016). The tests are thus considered relevant for assessment of the skin sensitisation potential of the notified chemical (LTD/2090), along with other supporting information.

The *in chemico* direct peptide reactivity assay (DPRA) aims to address the first key event (molecular initiation) of the AOP by measuring the interaction of the test substance with cysteine and lysine, small synthetic peptides representing the nucleophilic centres in skin proteins. The ARE-Nrf2 Luciferase Assay aims to address the second key event (keratinocyte activation) of the AOP by measuring the expression of a report luciferase gene under the control of a promoter from the antioxidant response element (ARE), a responding gene known to be upregulated by contact sensitisers. The *in vitro* h-CLAT assay aims to address the third key event (dendritic cell activation) of the AOP by measuring the expression of cell surface markers (such as CD54 and CD86) in human monocyte leukaemia cells (THP-1) upon stimulation with the test substance.

According to the OECD test guidelines (TG 442c, 442d and 442e), the suite of tests based on the AOP may not detect pre-haptens (chemicals that become sensitisers following auto-oxidation) and pro-haptens (chemicals requiring enzymatic activation to become sensitisers).

Out of the three key event assays in the AOP for skin sensitisation, the notified chemical LTD/2090 showed only one positive response (in the ARE-Nrf2 Luciferase assay: second key event of the AOP). The results of the first key event assay (DPRA) was inconclusive due to observed phase separation in the study. The third key event assay (h-CLAT) also gave negative results, however because of the measured log Pow of 5.02 of the notified chemical (LTD/2090), the result obtained could be a false negative. The OECD test guideline TG 442e suggests that negative results in the h-CLAT on test chemicals with a log Pow >3.5 should not be considered as a reliable outcome.

Therefore, based on the results of the three key events assays, a skin sensitisation potential for the notified chemical LTD/2090 cannot be ruled out.

Some of the expected degradants of both notified chemicals are aldehydes, which have structural alerts for skin sensitisation.

Repeated Dose Toxicity
No information was provided.

Mutagenicity
Both notified chemicals showed negative results in bacterial reverse mutation assays tested up to 5,000 µg/plate (LTD/2085) and 5 µL/plate (LTD/2090) respectively, with or without metabolic activation.

Health Hazard Classification
Based on the available information, the notified chemicals cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*, as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation
Skin sensitisation potential of the notified chemicals cannot be ruled out, and degradation products may also be sensitising.

6.3.1. Occupational Health and Safety
Transport, Storage and Reformulation
Exposure of workers to the notified chemicals (at ≤ 12% concentration for each chemical) may occur during transport and blending operations. During reformulation, worker exposure will be limited through the use of engineering controls (such as enclosed, automated systems and local exhaust ventilation) and appropriate PPE (eye/skin protection and respiratory protection if inhalation exposure may occur), as stated by the notifier. Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemicals are not considered to pose an unreasonable risk to the health of workers.

End-Use
Workers involved in professions where the services provided involve the use of household cleaning products in the cleaning industry may be exposed to the notified chemicals at ≤ 0.1% concentration (for each chemical). PPE may be employed by workers to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that for consumers using various cleaning products containing the notified chemicals. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health
Members of the public may experience frequent incidental exposure to the notified chemicals at ≤ 0.1% concentration (for each chemical) through use of household laundry and cleaning products. The main routes of exposure are expected to be dermal and inhalation, with some potential for accidental ocular exposure. Dermal exposure to low levels of degradants of the notified chemicals from the washed fabrics and surfaces cleaned may also be possible.

The notified chemicals and degradants may have skin sensitisation potential. However, risk of skin sensitisation is not expected at the proposed low concentrations (≤ 0.1%) of the notified chemicals in end-use products and the type of use.

When used in the proposed manner, the notified chemicals are not considered to pose an unreasonable risk to public health.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemicals will be imported as a component of a fragrance precursor formulation for reformulation into finished household laundry and cleaning products (such as laundry detergents, fabric softeners and hard surface cleaners) and in finished end use products. It is unlikely that there will be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the products containing the notified chemicals are expected to be collected with adsorbents and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated and is expected to occur within fully enclosed systems. Therefore, significant release of the notified chemicals from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail use. Wastes containing the notified chemicals generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. It is estimated that up to 0.2% of the import volume of the notified chemical (or up to 20 kg) may be released from reformulation and cleaning operations. Any wash waters resulting from the blending and cleaning operations are likely to be discharged to an on-site wastewater treatment plant before being discharged to sewer. Empty import containers are expected to be recycled or disposed of through licensed waste management services.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemicals are expected to be released to sewer across Australia as a result of their use in laundry products. A small proportion of the notified chemicals are expected to be disposed of to landfill as residues in empty end-use containers.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the notified chemicals may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified chemicals in empty containers are likely either to share the fate of the container and be disposed of to landfill, or to be released to sewer when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemicals are expected to enter the sewer system through use as a component of household laundry and cleaning products, before potential release to surface waters nationwide. The notified chemicals are hydrolytically unstable and release the fragrances and another degradant during use and in environmental conditions. The notified chemicals are not considered to be readily biodegradable (6% in 28 days). Whilst the notified chemicals are not readily biodegradable, they are considered ultimately biodegradable and are not expected to bioaccumulate. For details of the environmental fate studies, refer to Appendix C.

The majority of the notified chemicals will be released to sewer after use. A small proportion of the notified chemicals may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation, or disposed to landfill as collected spills and empty containers. The notified chemicals have low water solubility and hydrolyse rapidly and are predicted to be hydrophobic. Therefore, in the wastewater treatment processes in the sewage treatment plant (STP), most of the notified chemicals are expected to degrade or partition to sludge or to suspended solids where it will be removed for disposal to landfill. In landfill the notified chemicals are expected to slowly decompose by abiotic and biotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the notified chemicals being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the notified chemicals into sewer systems nationwide over 365 days per annum. The extent to which the notified chemicals are removed from the effluent in STP processes based on the properties of the notified chemicals

have not been considered for this scenario, and therefore no removal of the notified chemicals during sewage treatment processes, is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume per chemical	1,000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of each chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release per chemical	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 per chemical	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 1000 L/m^2/year (10 ML/ha/year). The notified chemicals in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 0.0037 mg/kg for each chemical. The notified chemicals are not likely to accumulate in soil.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical (LTD/2085) are summarised in the table below. The notified chemicals are expected to degrade during the studies. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 > 110 mg/L (WAF)	Not harmful to fish up to the limit of its water solubility
Daphnia Toxicity	EC50 > 8 µg/L	Not toxic to aquatic invertebrates up to the limit of its water solubility
Algal Toxicity	EC50 > 3.8 µg/L	Not harmful to algae up to the limit of its solubility

Based on the above ecotoxicological endpoints, the notified chemicals and their degradants are not expected to be harmful to aquatic life up to the limit of their water solubility. Therefore, the notified chemicals are not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

A predicted no effect concentration (PNEC) has not been calculated as the notified chemicals are not considered to be harmful to aquatic life up to the limit of their solubility in water.

7.3. Environmental Risk Assessment

A risk quotient RQ (PEC/PNEC) could not be calculated as the notified chemicals are not harmful to aquatic life up to the limit of their solubility in water. Whilst the notified chemicals are not readily biodegradable, they are considered to be ultimately biodegradable, are hydrolytically unstable in environmental conditions and are not expected to bioaccumulate. Therefore, on the basis of the low hazard to aquatic organisms, the notified chemicals and their degradants are not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 79-85 °C (onset) (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.1 Melting/Freezing Temperature
Remarks	The Differential scanning calorimetry (DSC) method was used. In the first heating run where the test substance was cooled down to 5 °C and then heated up to 130 °C with 10 K/min, the test substance showed a melting between 52 °C and 94 °C. In the second heating run where the test substance was cooled down to -90 °C and then heated up to 150 °C with 10 K/min, there were a glass transition temperature between -24 °C and -22 °C and a crystallisation (the onset temperature between 49 °C and 56 °C) followed by melting (onset temperature between 79 °C and 85 °C).
Test Facility	Henkel (2009a)

Melting Point No melting between -90 and 90 °C (LTD/2090)

Method	OECD TG 102 Melting Point/Melting Range (1995) EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	The DSC method was used. The test substance showed no melting or crystalline components in two heating runs between -90 and 90 °C. The test substance is a fluid at ambient temperature. The cooling run showed no crystallisation. At -26 °C, the test substance showed a glass transition temperature for amorphous components.
Test Facility	Henkel (2018a)

Boiling Point 322 °C at 102.1 kPa (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.2 Boiling Temperature
Remarks	The DSC method was used. The test substance was cooled down to 5 °C and then heated up to 430 °C with 10 K/min. The test showed a boiling/thermal decomposition from 322 °C with evaporation of the decomposition products. The DSC results were confirmed by the thermogravimetric analysis under the same test conditions, with a slight weight loss of 2.8% noted up to the beginning of boiling/decomposition.
Test Facility	Henkel (2009b)

Boiling Point 312 °C at 100.2 kPa (LTD/2090)

Method	OECD TG 103 Boiling Point (1995) EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	The DSC method was used. The test substance was cooled down to 5 °C and then heated up to 500 °C with 10 K/min. Boiling and/or thermal decomposition occurred from 312 °C. The DSC results were confirmed by thermogravimetric analysis under the same test conditions.
Test Facility	Henkel (2018b)

Density 1,032 kg/m^3 at 20 °C (LTD/2085)

Method	Similar to EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	The pycnometer method was used.
Test Facility	Henkel (2009c)

Density 1,059 kg/m^3 at 20 °C (LTD/2090)

Method	OECD TG 109 Density of Liquids and Solids
Remarks	The oscillating densitometer method was used.
Test Facility	Henkel (2018c)

Vapour Pressure ≤ 3.7×10^{-5} kPa at 20 °C (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.4 Vapour Pressure
Remarks	The DSC method was considered unsuitable. The vapour pressure calculation was based on the lowest possible boiling temperature using Grain Watson estimation.
Test Facility	Henkel (2009d)

Vapour Pressure ≤ 1.2×10^{-4} kPa at 20 °C (LTD/2090)
≤ 1.9×10^{-3} kPa at 50 °C (LTD/2090)

Method	OECD TG 104 Vapour Pressure (2006) EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	The DSC method was considered unsuitable. The vapour pressure calculation was based on the lowest possible boiling temperature using Grain Watson estimation.
Test Facility	Henkel (2018d)

Water Solubility Unstable in aqueous medium (LTD/2085)

Method	EU test method L383 A/54-62 (EU A.6).
Remarks	A preliminary study indicated that the water solubility of the test substance was below 10 mg/L. Therefore, the column elution method was used. The test substance degraded during column elution and therefore, the test was aborted.
Test Facility	Henkel (2009e)

Partition Coefficient (n-octanol/water) log Pow > 5.7 at 40 °C (LTD/2085)

Method	EU test method L383 A/63-73 (EU A. 8).
Remarks	The preliminary test using HPLC indicated the log Pow for the test substance to be > 5.7.
Test Facility	Henkel (2009f)

Partition Coefficient (n-octanol/water) log Pow = 5.02 at 40 °C (LTD/2090)

Method	OECD test method 117
Remarks	The preliminary test using HPLC indicated the test substance elutes with five peaks giving five log Pow values. Therefore, the weighted average log Pow was calculated to be 5.02.
Test Facility	Henkel (2018e)

Particle Size Not determined (LTD/2085)

Method	DIN 66165
Remarks	The test substance is a waxy solid at room temperature.
Test Facility	Henkel (2009g)

Flash Point 194 °C at 101.3 kPa (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.9 Flash Point
Remarks	Raid RT-1 tester according to DIN EN ISO 3678 was used. As the test substance is a solid at room temperature, it was fused at 105 °C for the measurement.
Test Facility	Henkel (2009h)

Flash Point 193 °C at 101.3 kPa (LTD/2090)

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	The test substance is a liquid at room temperature. Setaflash Serie 8 apparatus according to DIN EN ISO 3679 was used. An additional measurement of OptiFlash Standard (according to DIN EN ISO 2719) showed no flash point up to 200 °C.
Test Facility	Henkel (2018f)

Solid Flammability Not flammable (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.10 Flammability (Solids)
Remarks	Details of the results were not provided in the study report.
Test Facility	Henkel (2009i)

Flammability (Contact with Water) Not flammable (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.12 Flammability (Contact with Water)
Remarks	Details of the study were not included in the test report. Gas was generated after mixing with distilled water at 20°C at 0.133 L/kg/h. As the volume generated was < 1 L/kg/h, the criteria for a positive test was not met.
Test Facility	Henkel (2009j)

Flammability (Contact with Water) Not flammable (LTD/2090)

Method	EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water)
Remarks	Details of the study were not included in the test report. Gas was generated after mixing with distilled water at 20°C. As the volume generated was < 1 L/kg/h, the criteria for a positive test was not met.
Test Facility	Henkel (2018g)

Autoignition Temperature > 400 °C (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.16 Relative Self-Ignition Temperature for Solids
Remarks	No autoignition was detected up to the temperature of 400 °C reached in the study.
Test Facility	Henkel (2009k)

Autoignition Temperature 395 °C (LTD/2090)

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	The lowest temperature from a series of three measurements was rounded down to the nearest number divisible by 5.
Test Facility	Henkel (2018h)

Explosive Properties Not explosive (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.14 Explosive Properties.
Remarks	Thermal sensitivity was tested by an external laboratory, with negative results. Mechanical sensitivity with respect to shock was tested, with negative results. Mechanical sensitivity with respect to friction was not tested.
Test Facility	Henkel (2010)

Explosive Properties Not explosive (LTD/2090)

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	Thermal sensitivity (tested by an external laboratory) and mechanical sensitivity to shock both gave negative results.
Test Facility	Henkel (2018i)

Oxidizing Properties No oxidising properties (LTD/2085)

Method	EEC-directive 92/69/EEC, method A.17 Oxidizing Properties (Solids)
Remarks	Details of the study were not included in the test report.
Test Facility	Henkel (2009l)

Oxidizing Properties No oxidising properties (LTD/2090)

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks	Details of the study were not included in the test report.

Test Facility Henkel (2018j)

Pyrophoric Properties No pyrophoric properties (LTD/2085)

Method EEC-directive 92/69/EEC, method A.13 Pyrophoric Properties of Solids and Liquids
Remarks Details of the study were not included in the test report.
Test Facility Henkel (2009m)

Pyrophoric Properties No pyrophoric properties (LTD/2090)

Method EC Council Regulation No 440/2008 A.13 Pyrophoric Properties of Solids and Liquids
Remarks Details of the study were not included in the test report.
Test Facility Henkel (2018k)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001) EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/RccHan: WIST (SPF)
Vehicle	Corn oil
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	> 2,000 mg/kg bw
Signs of Toxicity	There were slight sedation, slightly ruffled fur and poor coordination observed in all females several hours following the treatment until day 2. There were slight to moderate sedation, ruffled fur and poor coordination observed in all males several hours after the treatment. All males showed hunched posture and one male showed ventral recumbency 5 hours after treatment. This latter male had ruffled fur, hunched posture, moderate sedation, ocular opacity, and red secretion from nose on day 2 while the others had slightly ruffled fur. Only one male had ruffled fur and hunched posture on day 3. All effects disappeared from day 4.
Effects in Organs	There were no macroscopic observations at necropsy.
Remarks – Results	Bodyweight gain was normal.

CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Harlan (2009a)

B.2. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical (LTD/2090)
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure (2001)
Species/Strain	Rat/WISTAR Crl: WI(Han)
Vehicle	Corn oil
Remarks – Method	No protocol deviations. One female was tested in the sighting study (group 1) while 4 other females were tested in the main study (group 2).

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	1 F	2,000	0/1
2	4 F	2,000	0/4

LD50	> 2,000 mg/kg bw (highest dose tested)
Signs of Toxicity	No signs of toxicity were noted.
Effects in Organs	There were no substance related macroscopic observations at necropsy.
Remarks – Results	Bodyweight gain was normal.

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

TEST FACILITY BSL Bioservice (2018)

B.3. Skin Irritation – *In Vitro* Reconstructed Human Epidermis Test Method

TEST SUBSTANCE Notified chemical (LTD/2085)

METHOD OECD Guideline for the Testing of Chemicals, Draft Proposal for a New Guideline, *In Vitro* Skin Irritation: Reconstructed Human Epidermins (RhE) Test Method, 20 March 2009, Vers. 6. (similar to OECD TG 439)

Vehicle None

Remarks – Method The Episkin model was used. Deionised water was used as the negative control and 5% sodium lauryl sulfate (SLP) as the positive control. The formazan reagent was extracted in the refrigerator and not at room temperature. This minor deviation did not affect the validity of the study.

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RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	0.8241 ± 0.0591	100	7.2
Test substance	0.7870 ± 0.0551	95.5	6.7
Positive control	0.1331 ± 0.0095	16.2	1.2

OD = optical density; SD = standard deviation

Remarks – Results The MTT-reducing capacity of the test substance was tested and found to be negative.

CONCLUSION Based on the mean tissue viability of > 50%, the notified chemical is not considered as irritating to the skin to classify it as a skin irritant according to the GHS criteria.

TEST FACILITY Harlan (2009b)

B.4. Skin Irritation – *In Vitro* Human Skin Model Test (EpiDerm™)

TEST SUBSTANCE Notified chemical (LTD/2090)

METHOD OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2015)

Vehicle None

Remarks – Method The negative control was Dulbecco's phosphate buffered saline and the positive control was 5% sodium dodecyl sulfate.

RESULTS

Test 1

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	1.838 ± 0.115	100	6.2
Test substance	0.898 ± 0.329	48.9	17.9
Positive control	0.090 ± 0.003	4.9	0.2

OD = optical density; SD = standard deviation

Test 2

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	1.755 ± 0.113	100	6.5
Test substance	1.012 ± 0.060	57.7	3.4
Positive control	0.061± 0.009	3.5	0.5

OD = optical density; SD = standard deviation

Test 3

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	2.705 ± 0.159	100	7.7
Test substance	1.508 ± 0.142	72.7	6.8
Positive control	0.094 ± 0.005	4.5	0.3

OD = optical density; SD = standard deviation

Remarks – Results

The test substance had a relative mean viability of < 50% (48.9%) in Test 1, and > 50% in Tests 2 and 3 (57.7 and 72.7% respectively). The test substance showed no non-specific reduction of MTT and no relevant colouring potential after mixing with distilled water and isopropanol.

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

CONCLUSION

Based on the mean tissue viability of > 50% in 2/3 tests, the notified chemical is not is not considered as irritating to the skin to classify it as a skin irritant according to the GHS criteria.

TEST FACILITY

Eurofins BioPharma (2019a)

B.5. Eye Irritation – *In Vitro* Hen's Egg Test - Chorioallantoic Membrane (HET-CAM Test)

TEST SUBSTANCE

Notified chemical (LTD/2085)

METHOD

In vitro Eye Irritation Test: Hen's Egg Test - Chorioallantoic Membrane (HET-CAM Test) INVITTOX Protocol No. 47:

Vehicle

None

Remarks – Method

No protocol deviations. Physiological sodium chloride solution (0.9% w/v in deionised water) was used as a negative control and 1% solutions of sodium dodecyl sulphate (SDS) and 0.1 N sodium hydroxide (NaOH) were used as positive controls.

RESULTS

Test substance	*Number of samples*	*Average score (irritation index)*
Negative control	3	0.00
Test substance	6	0.00
Positive control (SDS)	3	9.92
Positive control (NaOH)	3	19.12

Remarks – Results

The calculated mean irritancy index of 0.00 indicated that no irritating effects to the eyes with the notified chemical following 5 min incubation.

The mean irritancy indices of the positive and negative controls were comparable with historical control data and were within the acceptance criteria.

CONCLUSION

Based on the mean irritancy index calculated, the notified chemical is not considered as irritating to the eyes to classify it as an eye irritant according to the GHS criteria.

TEST FACILITY

Harlan (2009c)

B.6. Skin Sensitisation – LLNA

TEST SUBSTANCE

Notified chemical (LTD/2085)

METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2002)
Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	Methyl ethyl ketone (MEK)
Preliminary study	A pre-test was conducted to determine the highest non-irritant test concentration using two animals treated with 10% and 25% concentrations of the test substance on three consecutive days. There were clinical signs within 1 hour, 24 ± 4 hours and day 7. There was no signs of irritation or systemic toxicity.
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde in acetone:olive oil (4:1).
Remarks – Method	A solubility experiment determined that the highest concentration that could be formulated was 25% in MEK, which performed better than other solvents tested. Minor deviations on husbandry conditions including the relative humidity and temperature did not affect the validity of the study.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (S.I.) (test/control ratio)*
Test Substance			
0 (vehicle control)	4 F	596.1	-
5	4 F	661.5	1.11
10	4 F	524.0	0.88
25	4 F	431.4	0.72
Positive Control			
0	not reported	727.6	
5	not reported	1303.6	1.79
10	not reported	1518.4	2.09
25	not reported	4976.6	6.84

Remarks – Results	There were no deaths during the study. Some clinical signs were observed, but details were not provided. Body weights were within the normal range.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical up to the concentration tested.
TEST FACILITY	Harlan (2009d)

B.7. Skin Sensitisation – *In Chemico* DPRA Test

TEST SUBSTANCE	Notified chemical (LTD/2090)
METHOD	OECD TG 442c *In Chemico* Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA) (2015)
Vehicle	Acetonitrile
Positive Control	Cinnamic aldehyde ((2*E*)-3-phenylprop-2-enal)
Remarks – Method	No protocol deviations.

RESULTS

Sample	*Cysteine Peptide Depletion (% ± SD)*	*Lysine Peptide Depletion (% ± SD)*
Test Substance	9.14 ± 4.27	0.00 ± 0.00
Positive Control	69.38 ± 0.58	66.34 ± 0.83

SD = Standard Deviation

Remarks – Results	For the 100 mM stock solution of the test substance no phase separation or precipitation was observed, however there was cloudiness when diluted

with the lysine peptide solution. After the 24 h ± 2 h incubation period but before the HPLC analysis samples were inspected for precipitation, cloudiness or phase separation. Phase separation was observed for all samples, such as the test substance and positive control including the co-elution control. Samples were not centrifuged prior to the HPLC analysis.

No co-elution of the test item with any peptide peaks was observed.

The test substance had minimal reactivity to the synthetic peptides. However, since a phase separation with both peptides was noted, no firm conclusion can be made on the lack of reactivity.

CONCLUSION Although there was no reactivity with the peptides, due to the phase separation observed with both peptides, the results are not conclusive.

TEST FACILITY Eurofins BioPharma (2019b)

B.8. Skin Sensitisation – *In Vitro* ARE-Nrf2 Luciferase Test

TEST SUBSTANCE Notified chemical (LTD/2090)

METHOD OECD TG 442d *In Vitro* Skin Sensitisation Assays Addressing the AOP Key Event on Keratinocyte Activation (2018)
- The ARE-Nrf2 luciferase KeratinoSens™ test method (Appendix IA)

Vehicle Dimethyl sulfoxide (DMSO)
Positive Control Cinnamic aldehyde
Remarks – Method No protocol deviations.

RESULTS

Average of three experiments			
Sample	*Concentration (µM)*	*Mean Cell viability over experiments 1, 2 and 3 (% ± SD)*	*Mean Luciferase Induction over experiments 1, 2 and 3 (% ± SD)*
Negative Control	-	100 ± 0.0	1.00 ± 0.00
Test substance			
Dose Level 1	0.98	97.1 ± 1.7	1.25 ± 0.07
Dose Level 2	1.95	111.4 ± 9.5	1.09 ± 0.02
Dose Level 3	391	112.3 ± 11.6	1.27 ± 0.08
Dose Level 4	7.81	123.0 ± 15.8	1.54 ± 0.21
Dose Level 5	15.63	102.3 ± 36.2	2.23 ± 0.37
Dose Level 6	31.25	42.6 ± 21.4	5.00 ± 2.13
Dose Level 7	62.50	9.2 ± 6.7	2.80 ± 1.80
Dose Level 8	125.00	1.2 ± 1.5	0.41 ± 0.42
Dose Level 9	250.00	0.3 ± 0.4	0.01 ± 0.01
Dose Level 10	500.00	1.2 ± 2.0	0.00 ±0.00
Dose Level 11	1,000.00	1.0 ± 1.5	0.00 ± 0.00
Dose Level 12	2,000.00	0.7 ± 1.0	0.00 ± 0.00
Positive Control			
Dose Level 1	4.00	97.5 ± 3.1	1.20 ± 0.03
Dose Level 2	8.00	102.0 ± 7.1	1.36 ± 0.05
Dose Level 3	16.00	99.7 ± 8.6	1.52 ± 0.06
Dose Level 4	32.00	93.5 ± 20.6	1.98 ± 0.15
Dose Level 4	64.00	79.0 ± 8.3	3.59 ± 0.22

SD = Standard Deviation

Remarks – Results In experiment 1, a maximum luciferase activity (Imax) induction of 2.90 was measured at 31.25 µM with the cell viability of 19.5%. The lowest concentration with a significant luciferase induction > 1.5 (1.88) was 15.63

	µM with the cell viability being < 70% (60.6%). The EC1.5 was < 1,000 µM (8.16 µM). The positive result of > 1.5 induction was not considered valid, as at this concentration the cell viability was below the required level of 70%. Therefore in this experiment the test substance was not considered a sensitiser. In experiment 2, Imax induction of 4.93 was measured at a 31.25 µM with the cell viability at 61.6%. The lowest tested concentration with a significant luciferase induction > 1.5 (2.17) was 15.63 µM with the cell viability being > 70% (125%). The EC1.5 was < 1,000 µM (9.18 µM). The test substance was considered a sensitiser. Experiment 3 was performed because tests 1 and 2 had contradictory results. In test 3, Imax induction of 7.16 was measured at 31.25 µM with the cell viability of 46.8%. The lowest tested concentration with a significant luciferase induction > 1.5 (1.77) was 7.81 µM, followed by 15.63 µM (2.62) with the cell viabilities being > 70% (138.7% and 121.4). The EC1.5 was < 1,000 µM (5.25 µM). The test substance was considered a sensitiser. Overall there was a statistically significant dose response for luciferase activity induction in 2/3 experiments.
CONCLUSION	The test substance was considered positive in the second key event (keratinocytes response) of the adverse outcome pathway (AOP) for skin sensitisation as defined in the test guideline.
TEST FACILITY	Eurofins BioPharma (2019c)

B.9. Skin Sensitisation – *In Vitro* Human Cell Line Activation Test (h-CLAT)

TEST SUBSTANCE	Notified chemical (LTD/2090)
METHOD	OECD TG 442e *In Vitro* Skin Sensitisation Assays Addressing the Key Event on Activation of Dendritic Cells on the Adverse Outcome Pathway for Skin Sensitisation *In Vitro* Skin Sensitisation (2018) - Human Cell Line Activation Test (h-CLAT)
Vehicle	Dimethyl sulfoxide (DMSO)
Medium Control	Cell culture medium
Positive Control	2,4-Dinitrochlorobenzene (DNCB)
Remarks – Method	No protocol deviations.

RESULTS

Test 1

Sample	*Concentration (µg/mL)*	*Mean RFI* CD86 (%)*	*Mean RFI* CD54 (%)*	*Relative Cell Viability (%)*	
				CD86	CD54
Medium Control	-	107	81	96.5	96.8
Vehicle Control	0.20%	100	100	96.2	96.1
Test substance					
Dose Level 1	39.88	66	134	85.7	86.3
Dose Level 2	33.23	74	90	88.3	86.9
Dose Level 3	27.69	86	105	91.0	91.0
Dose Level 4	23.08	78	86	90.8	91.9
Dose Level 5	19.23	113	83	90.7	90.7
Dose Level 6	16.03	147	95	91.3	91.8
Dose Level 7	13.36	139	104	91.7	91.8
Dose Level 8	11.13	123	95	91.3	91.5
Positive Control	4.00	280	321	82.9	84.5

* RFI = relative fluorescence intensity

Test 2

Sample	*Concentration (µg/mL)*	*Mean RFI* CD86 (%)*	*Mean RFI* CD54 (%)*	*Relative Cell Viability (%)*	
				CD86	CD54
Medium Control	-	115	90	96.8	96.7
Vehicle Control	0.20%	100	100	96.9	96.9
Test substance					
Dose Level 1	39.88	130	105	84.1	84.4
Dose Level 2	33.23	134	110	91.8	92.6
Dose Level 3	27.69	111	121	95.9	95.7
Dose Level 4	23.08	133	145	95.7	96.0
Dose Level 5	19.23	100	93	95.9	96.2
Dose Level 6	16.03	117	109	97.0	97.3
Dose Level 7	13.36	115	97	96.2	96.5
Dose Level 8	11.13	126	100	96.3	96.7
Positive Control	4.00	394	281	90.9	90.7

* RFI = relative fluorescence intensity

Remarks – Results	Relative cell viability at the highest concentrations tested decreased to < 90%: to 85.7% (CD86) and 86.3% (CD54) in test 1 and to 84.1% (CD86) and 84.4% (CD54) in test 2. In both tests, the expression of the cell surface marker CD86 did not increase to above the threshold of 150% and the expression of the cell surface marker CD54 did not increase to above the threshold of 200%. In each case the relative cell viability of the highest dose tested was < 90%, which is requirement according to the TG if the test result is negative. Other acceptability criteria for the test were satisfied, including results for controls. According to the Test Guideline, the results of this test may not be valid, because the result is negative but the log Pow of the test substance is > 3.5 (the test is recommended for chemicals with log Pow < 3.5).
CONCLUSION	The test substance was considered negative in the third key event (dendritic cell activation) of the adverse outcome pathway (AOP) for skin sensitisation as defined in the test guideline.
TEST FACILITY	Eurofins BioPharma (2019d)

B.10. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Plate incorporation procedure (test 1)/Pre incubation procedure (test 2)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	Phenobarbital/ß-Naphthoflavone induced rat liver S9
Concentration Range in Main Test	Test 1: 0, 3, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate Test 2: 0, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate
Vehicle	Dimethylformamide (DMF)
Remarks – Method	No protocol deviations. Test 1 was used as the pre-test.

RESULTS

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

Remarks – Results

The test substance did not induce increases in the number of revertant colonies in the plate incorporation or pre-incubation assay, at any dose level, in any tester strain, in the absence or presence of metabolic activation.

The concurrent positive and 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

RCC (2008)

B.11. Genotoxicity – Bacteria

TEST SUBSTANCE

Notified chemical (LTD/2090)

METHOD

OECD TG 471 Bacterial Reverse Mutation Test (1997)
Plate incorporation procedure (test 1)/Pre incubation procedure (test 2)

Species/Strain: *Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, TA102

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

Concentration Range in Main Test: With and without metabolic activation: 0, 0.0316, 0.100, 0.316, 1.0, 2.5 and 5.0 µL/plate

Vehicle: Dimethyl sulfoxide (DMSO)

Remarks – Method: *Escherichia coli* was not used. Doses were chosen on the basis of a preliminary experiment.

RESULTS

Metabolic Activation	*Test Substance Concentration (µL/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5			
Test 1		> 5	> 5	negative
Test 2		> 5	> 5	negative
Present	> 5			
Test 1		> 5	> 5	negative
Test 2		> 5	> 5	negative

Remarks – Results

The test substance did not induce increases in the number of revertant colonies in the plate incorporation or pre-incubation assay, at any dose level, in any tester strain, in the absence or presence of metabolic activation up to the dose tested.

The reduction in the number of revertants in test 2 in TA98 at concentrations of 1.0 and 5.0 µL/plate (without S9) was not considered biologically relevant by study authors due to lack of a dose-response relationship and associated clearing of background lawn.

	The concurrent positive and 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	Eurofins BioPharma (2019e)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution (Modified Sturm Test)
Inoculum	Activated sludge
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	Total Organic Carbon (TOC)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The test was performed with a nominal start concentration of ~20 mg organic carbon/L. An abiotic control was also run.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
4	0.3	4	17.6
11	3.1	11	69.4
23	5.2	23	78.3
29	5.5	29	80.2

Remarks - Results	All validity criteria for the test were satisfied. Therefore, the test indicates the suitability of the inoculums. The CO_2 evolution in the control was 7.9 mg/L. The toxicity control (containing test substance, positive control (aniline), mineral medium and inoculum) attained 42.9% degradation up to day 23. Therefore the notified chemical is not toxic to the sewage treatment micro-organisms used in the study. There was no abiotic degradation. The test substance attained 5.5% degradation after 29 days and, therefore, cannot be considered as readily biodegradable under the conditions of OECD Guideline 301B.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	LAUS (2009a)

C.2. Ecotoxicological Investigations

The notified chemicals are expected to degrade during the studies, but any toxicity of the degradants will be intrinsically determined during each study.

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 203 Acute Toxicity for Fish –Static
Species	Rare minnow (*Gobiocypris rarus*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	143 mg $CaCO_3$/L
Analytical Monitoring	Ultra-Performance LC (UPLC)

Remarks – Method	On the basis of the range finding test, a limit test was conducted. Due to poor solubility, a water accommodated fraction (WAF) was prepared. The notified chemical was added directly to the test medium, stirred for 24 hours and allow to settle for 1 hour. The fish were exposed to the limit concentration of 110 mg/L and a control. A positive control [(single treatment using potassium dichromate ($K_2Cr_2O_7$)] was run prior to the definitive study for quality assurance. The concentration of the notified chemical was measured at the start of the study and daily thereafter, until study termination.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
0	< LOQ	7	0
110 (WAF)		7	0

WAF = Water Accommodated Fraction
LOQ not recorded

LC50	> 110 mg/L (WAF) at 96 hours
NOEC	≥ 110 mg/L (WAF) at 96 hours
Remarks – Results	All validity criteria were met. Dissolved Oxygen (DO) values varied from 75% and 95%. All results were within 80% of the initial concentration indicating the notified chemical is sufficiently stable in water during the test period, to use the static test protocol. The 24-hour LC50 of the positive control was 325 mg/L, which was within the accepted range. No abnormal behaviour was observed in any of the treatments.

CONCLUSION	The notified chemical is not toxic to fish to the limits of its water solubility.
TEST FACILITY	PEAPC (2016)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia – Semi Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Methanol
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography (GC)
Remarks - Method	On the basis of low water solubility, a limit test was conducted. A stock solution containing 18 mg/L of the test substance in methanol was prepared. The main study was performed as a limit test using one concentration in the range of water solubility. The water solubility was determined as approximately 8 µg/L. A positive control using $K_2Cr_2O_7$ was run. The test media containing the test substance were replaced daily.

RESULTS

Concentration µg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Geometrical mean measured*		*24 h*	*48 h*
Control (0)	ND	20	0	0
Solvent Control (0)	ND	20	0	0

8	20	0	0

ND = Not determined

LC50	> 8 µg/L at 48 hours
NOEC	≥ 8 µg/L at 48 hours
Remarks - Results	All validity criteria were met. Dissolved Oxygen (DO) values was maintained at 8.7 mg/L The temperature was maintained at ± 20 °C. The 24-hour LC50 of the positive control was 1.6 mg/L. No abnormal behaviour was observed in any of the treatments.
CONCLUSION	The notified chemical is not toxic to daphnia up to the limits of its water solubility.
TEST FACILITY	LAUS (2009b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical (LTD/2085)
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	Green alga (*Desmodesmus subspicatus)*
Exposure Period	72 hours
Concentration Range	Actual: 8 µg/L
Auxiliary Solvent	None
Water Hardness	Not given
Analytical Monitoring	LC-MS/MS
Remarks - Method	On the basis of low water solubility, a limit test was conducted. A stock solution containing 200 mg/L of the test substance in methanol was prepared. The main study was performed as a limit test using one concentration in the range of water solubility. The water solubility was determined as approximately 8 µg/L. A positive control using $K_2Cr_2O_7$ was run.

RESULTS

Biomass		*Growth*	
EbC50 *µg/L at 72 h*	*NOEC* *µg/L at 72 h*	*ErC50* *µg/L at 72 h*	*NOEC* *µg/L at 72 h*
> 3.8	≥ 3.8	> 3.8	≥ 3.8

Remarks - Results	The validity criteria were satisfied. The cell concentration in the control grew by a factor of 116. The mean coefficient of variation of daily growth rates was 35%. The coefficient of variation of average maxima was 2%. The EC50s of the positive control was within the normal range for the laboratory.
CONCLUSION	The notified chemical is not toxic to algae up to the limits of its water solubility.
TEST FACILITY	LAUS (2009c)

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