File No.: LTD/2073

June 2019

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

6,10-Dodecadien-1-ol, 3,7,11-trimethyl-, (3*S*,6*E*)-

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	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2073	Takasago International (Singapore) Pte Ltd	6,10-Dodecadien-1-ol, 3,7,11-trimethyl-, (3*S*,6*E*)-	Yes	< 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard Classification	*Hazard Statement*
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

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

Hazard Classification	*Hazard Statement*
Acute Aquatic Toxicity (Category 1)	H400 - Very toxic to aquatic life

Human Health Risk Assessment
Provided that the recommended controls are being adhered to, 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, 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 irritation (Category 2): H315 – Causes skin irritation
  - Sensitisation, skin (Category 1B): H317 – May cause an allergic skin reaction

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

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

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

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 physical containment, collection and subsequent safe disposal.

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.

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 final use concentration of the notified chemical exceeds 0.05% in cosmetic and household products;

or

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

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

Safety Data Sheet
The SDS of the notified chemical 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
Takasago International (Singapore) Pte Ltd (ABN: 29 099 666 832)
Level 5, 815 Pacific Highway
CHATSWOOD NSW 2067

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 exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are varied for melting/freezing point, hydrolysis as a function of pH, dissociation constant, flammability, explosive properties and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
EU (2018)
USA (2006)
China (2013) and Philippines (2000) for 6,10-dodecadien-1-ol, 3,7,11-trimethyl- (CAS Number: 51411-24-6)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Biocyclamol

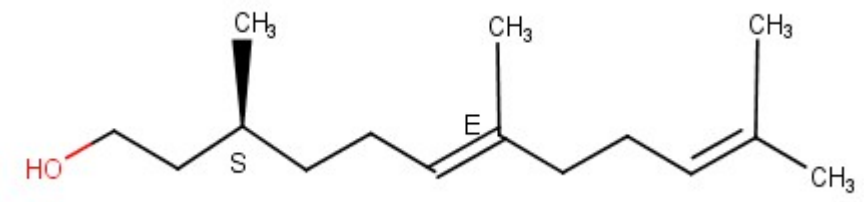
CAS NUMBER
27745-36-4

CHEMICAL NAME
6,10-Dodecadien-1-ol, 3,7,11-trimethyl-, (3*S*,6*E*)-

OTHER NAMES
L-Dihydrofarnesol
(-)-DH-Farnesol

MOLECULAR FORMULA
$C_{15}H_{28}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
224.38 g/mol

ANALYTICAL DATA

METHOD	GC-FID (achiral) – no separation of optical isomers
Remarks	Main peak (98.45%) ascribed to the notified chemical plus its optical isomer, and 12 small peaks (max. 0.3% each, 1.55% in total) ascribed to unidentified impurities
TEST FACILITY	Takasago International corporation (2016)
METHOD	GC-FID (chiral) – separation of optical isomers
Remarks	The main peak above was determined to consist of 97.91% (notified chemical) and 2.09% 6,10-Dodecadien-1-ol, 3,7,11-trimethyl-, (3R,6E)- (CAS No. 34083-92-6)
TEST FACILITY	Takasago International corporation (2016)
METHOD	Optical activity
Remarks	Specific rotation: -4.0 °C. A negative value is in agreement with the chirality of the notified chemical
TEST FACILITY	Takasago International corporation (2016)
METHOD	GC-MS
Remarks	Spectra consistent with structure of the notified chemical
TEST FACILITY	Takasago International corporation (2016)
METHOD	^{1}H and ^{13}C NMR
Remarks	Spectra consistent with the structure of the notified chemical.
TEST FACILITY	Takasago International corporation (2016)
METHOD	FT-IR
Remarks	Major peaks at: 3320, 2962-2915, 1450, 1376 and 1056 cm^{-1}. The IR-spectrum is consistent with that of the notified chemical
TEST FACILITY	Takasago International corporation (2016)
METHOD	UV/Vis
Remarks	UV absorbance at 202 nm. The UV spectrum is consistent with that of the notified chemical.
TEST FACILITY	Takasago International corporation (2016)

3. COMPOSITION

DEGREE OF PURITY
> 90%

IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name	6,10-Dodecadien-1-ol, 3,7,11-trimethyl-, (3*R*,6*E*)-		
CAS No.	34083-92-6	*Weight %*	2.06
Chemical Name	12 unidentified impurities		
CAS No.	-	*Weight %*	1.55 (max. 0.3% each)

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless to pale yellow liquid

Property	***Value***	***Data Source/Justification***
Melting Point/Freezing Point	Not determined	Liquid at room temperature
Boiling Point	298.8 °C at 101.3 kPa	Measured
Density	871 kg/m^3 at 20 °C	Measured
Vapour Pressure	9.13×10^{-6} kPa at 25 °C	Measured
Water Solubility	0.00308 g/L at 20 °C	Measured

Property	*Value*	*Data Source/Justification*
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functional groups
Partition Coefficient (n-octanol/water)	log P_{ow} = 5.7 at 25 °C	Measured
Adsorption/Desorption	log Koc = 4.2 at 25 °C	Estimated using ACD/Labs v11.02
Dissociation Constant	Not determined	Contains no dissociable functionalities in environmental pH range of 4 - 9
Flash Point	149 °C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be flammable
Autoignition Temperature	247 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties

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

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

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

The notified chemical has a flash point of 149 ºC which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the notified chemical may be considered as a Class C2 combustible liquid.

5. INTRODUCTION AND USE INFORMATION

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

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.1	0.1	0.1	0.3	0.5

PORT OF ENTRY
All major Australian ports

IDENTITY OF MANUFACTURER
Takasago International Corp. (Japan)

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of fragrance formulations in 200 L metal drums. Within Australia the drums will be transported mainly by road to the warehouse for storage and later distribution to the formulators by road for reformulation. Finished consumer products containing the notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in fine fragrances at < 0.05% concentration, and in cosmetic and household products at < 0.005% concentration.

OPERATION DESCRIPTION

Reformulation of fragrance formulations containing the notified chemical at < 5% concentration into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end-use products into containers of various sizes.

End-use products containing the notified chemical at < 0.05% concentration will be used by consumers and professionals such as hairdressers, beauticians or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	1-2	50
Mixers	≤ 8	240
Quality control	0.5	240
Cleaning and maintenance	≤ 8	240
Professional end users	1-8	200

EXPOSURE DETAILS

Transport and storage

Transport, storage and warehouse workers may come into contact with the notified chemical as a component of fragrance formulations at < 5% concentration, only in the unlikely event of accidental rupture of containers.

Reformulation

During reformulation, dermal and ocular exposure of workers to the notified chemical at < 5% concentration may occur during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. Due to the notified chemical's low vapour pressure (9.13×10^{-6} kPa at 25 °C), inhalation exposure is not expected, unless aerosols or mists are formed.

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

End-use

Exposure to the notified chemical in end-use products at < 0.05% concentration may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hair dressers and workers in beauty salons), or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular is also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical at < 0.05% concentration through the use of a wide range of cosmetic and household products. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Acute oral toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity
Skin corrosion – in vitro human skin model test	non-corrosive
Skin irritation – *in vitro* reconstructed human epidermis method	irritant
Skin irritation – human closed patch test	non-irritating at 2% concentration (n=30)
Eye irritation – *in vitro* bovine corneal opacity and permeability (BCOP) test	non-irritant
Skin sensitisation – mouse local lymph node assay	evidence of sensitisation (EC3=21.4%)
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics
Given the low molecular weight (224.38 g/mol), the notified chemical may be absorbed across the respiratory or gastrointestinal tract. Based on its low water solubility (0.003 g/L at 20 °C) and high partition coefficient (Pow = 5.7 at 25 °C) the notified chemical has a reasonably high lipophilicity, and hence percutaneous absorption is expected to be limited.

Acute Toxicity
The notified chemical was found to be of low acute oral toxicity in rats.

No acute dermal or acute inhalation toxicity data were provided of the notified chemical.

Irritation and Sensitisation
In *in vitro* skin irritation/corrosion studies, the notified chemical was found to be a skin irritant but non-corrosive. In a human patch test (n=30), a solution containing the notified chemical at 2% concentration was found to be non-irritating. Based on the results of the *in vitro* studies, the notified chemical should be classified as a Category 2 Skin Irritant according to the GHS criteria.

In an *in vitro* bovine corneal opacity and permeability (BCOP) test, the notified chemical was found not to warrant classification as an eye irritant under the GHS criteria.

The notified chemical was found to be a weak skin sensitiser in a mouse Local Lymph Node Assay (LLNA) with stimulation indices of 4.36, 10.36 and 13.71 at 25, 50 and 100% concentrations, respectively. The EC_3 value was calculated to be 21.4%.

Repeated dose toxicity
No information is available on the repeated dose toxicity of the notified chemical.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study.

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

Hazard Classification	*Hazard Statement*
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided, the notified chemical is considered a skin irritant and a weak skin sensitiser.

Reformulation

Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical at < 5% concentration during reformulation. Given the notified chemical is a skin sensitiser caution should be exercised when handling the notified chemical during reformulation processes. The use of local ventilation, enclosed/automated processes and PPE (i.e. coveralls, goggles, impervious gloves and respiratory protection, if inhalation exposure may occur), as stated by the notifier, should minimise the potential for exposure.

Therefore, provided control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical at ≤ 0.05% concentration, similar to public use. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the notified chemical up to 0.05% is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2 below.

6.3.2. Public Health
Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products containing the notified chemical at ≤ 0.05% concentration.

Acute toxicity and irritation
The notified chemical is a skin irritant. However, effects are not expected from the use of products containing the notified chemical at the proposed low use concentrations in cosmetic and household products.

Sensitisation
Based on the results of an LLNA study, the notified chemical is considered to be a weak skin sensitiser (EC_3 = 21.4%). Using deodorants as an example product that may contain the notified chemical at 0.05% concentration, as a worst case scenario, the Consumer Exposure Level (CEL) (Cadby *et al*., 2002) is estimated to be 0.38 μg/cm^2/day. Consideration of available information and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 15.53 μg/cm^2/day. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of deodorants (a worst case example of a leave-on cosmetic product) is not considered to be unreasonable. Based on lower expected exposure level from other cosmetic products and household products, by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. However, it is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Systemic Effects
The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low concentration of the notified chemical (≤ 0.05%) in end use products and the limited potential for dermal absorption.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.05% in cosmetic and 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 into Australia as a component of fragrance formulations for reformulation into finished cosmetic and household products. In general, the reformulation processes are expected to involve automated blending operations in an enclosed environment, followed by automated filling of the finished products into end-use containers. Wastes containing the notified chemical generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. These wastes will either be released

to sewers or disposed of to landfill according to local government regulations. Release of the notified chemical to the environment in the event of accidental spills or leaks during reformulation, storage and transport is expected to be collected for disposal, in accordance with local government regulations.

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

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

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system through its use in cosmetic formulations and household products, before potential release to surface waters nationwide. Based on the results of a ready biodegradability study, the notified chemical is considered readily biodegradable (99% in 28 days). For details of the environmental fate study, please refer to Appendix C. Based on its low water solubility (3.08 mg/L) and high adsorption coefficient (log K_{oc} = 4.2), if the notified chemical is released to surface waters it is expected to partition to sludge and sediment. 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 low measured vapour pressure (9.13×10^{-6} kPa at 25 °C) indicates that the notified chemical is slightly volatile and not expected to significantly partition to air at any stage during its lifecycle.

The majority of the notified chemical will be released to sewer after use. The notified chemical is expected to be efficiently removed (93%) through sewage treatment plant (STP) processes due to its limited water solubility, high partition coefficient (log P_{ow}) and ready biodegradability.

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. Removal at STP was determined using SimpleTreat 3.0 (Struijs, 1996).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	1000	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	24.386	million
Removal within STP	93	%
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC – River:	0.039	µg/L
PEC – Ocean:	0.004	µg/L

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 4.045 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1,500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.027 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application.

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

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity	48 h EC50 = 0.209 mg/L	Very toxic to aquatic invertebrates
Algal Toxicity	72 E_rC50 = 1.43 mg/L	Toxic to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be very 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 1; Very toxic to aquatic life".

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the Daphnid Acute Immobilisation Test. A safety factor of 500 was used given acute endpoints for two trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Daphnia, 48 h)	0.209	mg/L
Assessment Factor	500	
Mitigation Factor	1.00	
PNEC	0.418	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC (µg/L)	PNEC (µg/L)	Q
Q – River	0.039	0.418	**0.094**
Q – Ocean	0.004	0.418	**0.009**

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. On the basis of the PEC/PNEC ratio, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point 298.8 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point
Remarks	Capillary method
Test Facility	CERI (2017a)

Density 871 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Oscillating densitometer
Test Facility	CERI (2017b)

Vapour Pressure 9.13×10^{-6} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Gas saturation method
Test Facility	CERI (2017c)

Water Solubility 0.00308 g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Column Elution Method; column temperature was 40 °C
Test Facility	CERI (2017d)

Partition Coefficient (n-octanol/water) log P_{ow} = 5.7 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water)
Remarks	HPLC Method; column temperature was 25 °C
Test Facility	CERI (2017e)

Flash Point 149 °C at 101.3 kPa

Method	EEC – Directive 92/69 EEC A.9 Flash Point
Test Facility	NOTOX (1997)

Autoignition Temperature 247 °C

Method	ASTM E659-78 Standard Test Methods for Autoignition Temperature of Liquid Chemicals
Test Facility	CERI (2017f)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Wistar
- Vehicle: Not stated
- Remarks – Method: The test substance was administered via gavage.

RESULTS

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

- LD50: > 2,000 mg/kg bw
- Signs of Toxicity: No signs of toxicity were observed.
- Effects in Organs: Not stated
- Remarks – Results: The animals showed expected body weight gains during the observation period (14 days).

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

TEST FACILITY: TIC (1997)

B.2. Skin Corrosion – *In Vitro* Human Skin Model Test

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 431 *In vitro* Skin Corrosion – Human Skin Model Test
- Vehicle: Nil
- Remarks – Method: The EpiDerm (EPI-200) test system was used.

  Positive (5% sodium dodecyl sulphate) and negative (phosphate buffered saline) controls were run in parallel with the test substance.

  The optical densities were determined at 570 nm.

RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*		*Relative Mean Viability (%)*		*SD of Relative Mean Viability*	
	3 minute exposure	60 minute exposure	3 minute exposure	60 minute exposure	3 minute exposure	60 minute exposure
Negative control	2.287	2.146	100	100	0.00	0.85
Test substance	2.225	2.338	97.3	108.9	3.68	4.81
Positive control	0.190	0.069	8.3	3.3	0.14	0.21

OD = optical density; SD = standard deviation

- Remarks – Results: A preliminary test was performed which indicated that the test substance does not directly reduce MTT.

  The relative mean viability of the test substance treated tissues was 97.3% and 108.9% after 3 and 60 minute exposure periods, respectively.

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

A mean tissue viability of ≥ 50% (for 3 minute exposure) and ≥ 15% (for 60 minute exposure) is considered as non-corrosive.

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

TEST FACILITY CERI (2017h)

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

TEST SUBSTANCE Notified chemical

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

Vehicle Nil

Remarks – Method Positive (5% sodium dodecyl sulphate) and negative (phosphate buffered saline) controls were run in parallel with the test substance.

The optical densities were determined at 570 nm.

RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	1.787	100	3.7
Test substance	0.736	41.2	5.8
Positive control	0.024	1.3	0.2

OD = optical density; SD = standard deviation

Remarks – Results The EpiDerm (EPI-200) test system was used.

A preliminary test was performed which indicated that the test substance does not directly reduce MTT.

The relative mean viability of the test substance treated tissues was 41.2%. A mean tissue viability of ≤ 50% for the test substance is considered to be a skin irritant.

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

CONCLUSION Based on the mean tissue viability of ≤ 50%, the notified chemical should be classified for skin irritation (Category 2) according to the GHS criteria.

TEST FACILITY CERI (2017g)

B.4. Skin Irritation – Human Patch Test

TEST SUBSTANCE Notified chemical (2% in vehicle)

METHOD Human closed patch test

Study Design Patches containing the test substance (amount not stated) and vehicle control (lanolin) were applied separately to the upper arms of 30 subjects. The closed patches were removed after 45 hours and the application sites were evaluated at 5 hours and 27 hours after patch removal.

Study Group 13 F, 17 M; age range 23-57 years

Vehicle Lanolin

Remarks – Method Occluded

RESULTS

Remarks – Results	All 30 subjects completed the study. There were no skin reactions.

CONCLUSION	The test substance was non-irritating under the conditions of the test.
TEST FACILITY	TIC (1996)

B.5. Eye Irritation – *In Vitro* BCOP Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
Vehicle	Nil
Remarks – Method	Positive (dimethylformamide) and negative (distilled water) controls were run in parallel with the test substance.

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues*	*Mean Permeabilities of Triplicate Tissues*	*IVIS*
Negative control	0.7	0.002	0.7
*Test substance**	-0.4	0.000	-0.4
*Positive control**	73.0	0.872	86.1

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

Remarks – Results	The IVIS of the test substance was -0.4. An IVIS ≤ 3 is considered as a non-irritant. The controls gave satisfactory results confirming the validity of the test system.
CONCLUSION	The notified chemical was not considered an eye irritant under the conditions of the test.
TEST FACILITY	SRICCCL (2017)

B.6. Skin Sensitisation – LLNA

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Diethyl phthalate/ethanol (3:1)
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde, technical (85%) in diethyl phthalate/ethanol (3:1). Not conducted in parallel with the test substance.
Remarks – Method	A preliminary test was conducted using undiluted test substance to justify the dose concentrations for the main study.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	5 F	634.70	-
25	5 F	2768.14	4.36

50	5 F	6573.41	10.36
100	5 F	8704.87	13.71
Positive Control			
25	5 (sex not stated)	Not stated	5.52

EC3 21.4%

Remarks – Results No unscheduled mortalities or signs of systemic toxicity were observed during the study period.

The stimulation index was > 3 in all test groups, indicating a sensitising response. The EC_3 was calculated to be 21.4%.

Slight redness of the ears and neck was observed on days 3 (post-dose) and days 4-6 of observation in all animals exposed to the undiluted test substance.

Slight reduction in bodyweight gain was observed in a vehicle control animal, one mid-dose and two high-dose animals.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY Envigo (2016)

B.7. Genotoxicity – Bacteria

TEST SUBSTANCE Notified chemical

METHOD Standards for Mutagenicity Tests using Microorganisms (Notification No. 77, 1988, the Japanese Ministry of Labour).
Similar to OECD TG 471 Bacterial Reverse Mutation Test

Species/Strain *Salmonella typhimurium*: TA1535, TA1537, TA98, TA100
Escherichia coli: WP2uvrA

Metabolic Activation System S9 mix from phenobarbital/β-naphthoflavone induced rat liver

Concentration Range in Main Test a) With metabolic activation: 39.1, 78.1, 156, 313, 625and 1,250 µg/plate for TA100, 156, 313, 625, 1,250, 2,500 and 5,000 µg/plate for TA1535, TA98 and WP2uvrA and 2.44, 4.88, 9.77, 19.5, 39.1 and 78.1 for TA1537.

b) Without metabolic activation: 0.61, 1.22, 2.44, 4.88, 9.77 and 19.5 µg/plate for TA100, TA1535, TA98 and TA1537 and 156, 313, 625, 1,250, 2,500 and 5,000 µg/plate for WP2uvrA.

Vehicle Dimethyl sulfoxide (DMSO)

Remarks – Method 0.31, 1.22, 4.88, 19.5, 78.1, 313, 1,250 and 5,000 µg/plate was used in preliminary test 1 and 0.076, 0.305, 1.22, 4.88 and 19.5 µg/plate was used in preliminary test 2 (both with and without S9-mix).

Negative and positive controls were used in parallel with the test material.

Negative control: DMSO
Positive control: i)with S9-mix: 2-aminoanthracene and
ii)without S9-mix: sodium azide (TA1535); 9-aminoacridine (TA1537); and 2-(2-fryl)-3-(5-nitro-2-fryl)acrylamide (TA100, TA98 and WP2uvrA).

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				

Test 1†	≥ 19.5	≥ 9.77	> 19.5	negative
Test 2*	≥ 19.5	> 5,000	≥ 2,500	negative
Present				
Test 1	≥ 78.1	≥ 78.1	≥ 2,500	negative

†All strains, except for WP2uvrA
*WP2uvrA strain only

Remarks – Results	In Test 1 (without S9-mix) reduced background growth was observed with TA100, TA1535, TA98 and TA1537 at ≥ 9.77 µg/plate. In Test 1 (with S9-mix) reduced background growth was observed with TA1537 at 78.1 µg/plate, with TA100 at 625 µg/plate, with TA1535 at ≥ 2,500 µg/plate and with TA98 at ≥5,000 µg/plate with S9-mix. In Test 2 (without S9-mix) the test substance caused no visible reduction in the growth of the bacterial background lawn in WP2uvrA at any dose tested. No substantial increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose level either with or without S9-mix. The vehicle control plates gave counts of revertant colonies within the normal range. All of the positive controls used in the test induced marked increases in the frequency of revertant colonies, both with or without S9-mix, 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	TIC (2016)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Activated sludge prepared from 10 samples taken across different locations in Japan
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical Oxygen Demand (BOD) by oxygen consumption measuring apparatus, test substance by Gas Chromatography (GC)
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was directly added to the test vessels.

RESULTS

Test Substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	46	7	85
14	72	14	91
21	91	21	91
28	99	28	90

Remarks – Results	All validity criteria for the test were satisfied. The degree of degradation of the test substance after 28 days was 99% by BOD and 100 % by GC.
CONCLUSION	The test substance is readily biodegradable
TEST FACILITY	CERI (2016)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	32 mg $CaCO_3$/L
Analytical Monitoring	GC-MS
Remarks – Method	No major deviations from the test guideline were reported. A saturated stock solution of the tested chemical was prepared by mixing 100 mg of the chemical in 1 L of water; the final concentration reached the solubility limit. Aliquots of the stock solution were used to prepare test solutions with the desired concentration of the notified chemical. The test media was renewed after 24 hours. The test media was sampled at the start of the exposure, after renewal and at the end of the exposure for analysis of the test substance.

RESULTS

Geometric mean of measured concentrations (mg/L)	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0	0
0.126	20	0	0
0.217	20	0	11
0.421	20	5	20
0.763	20	18	20
1.37	20	20	20

EC50	0.209 mg/L at 48 hours (measured concentration)
Remarks – Results	All validity criteria for the test were satisfied. The dissolved oxygen concentration in the test solution during the test was ≥ 8.5 mg/L at 20 °C. No abnormal responses were observed in the control group.
CONCLUSION	The test substance is very toxic to aquatic invertebrates
TEST FACILITY	CERI (2017i)

C.2.2. Algal Growth Inhibition Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0.0457 – 4.57 mg/L Actual: 0.0247 – 2.76 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC-MS
Remarks – Method	A saturated stock solution of the test chemical was prepared by mixing 100 mg of the chemical in 1 L of water; the final concentration reached the solubility limit at 23 °C. Aliquots of the stock solution were used to prepare test solutions with the desired concentration of the notified chemical. Test solution concentrations are reported as the geometric mean of the concentrations measured at the start and end of experiment.

RESULTS

Biomass		*Growth*	
E_bC_{50} mg/L at 72 h	*NOEC mg/L*	*E_rC_{50} mg/L at 72 h*	*NOEC mg/L*
Nor reported		1.43	0.0774

Remarks – Results	All the validity criteria for the test were satisfied. The mean cell density in the control increased more than 16 times by 72 h.
CONCLUSION	The test substance is toxic to algae
TEST FACILITY	CERI (2017j)

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