File No: LTD/1971

April 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Glycine, *N*-[[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]carbonyl]-, ethyl ester

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1971	Procter & Gamble Australia Pty Ltd	Glycine, *N*-[[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]carbonyl]-, ethyl ester	ND*	≤ 1 tonne per annum	Toothpaste and mouth rinse ingredient

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

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

Hazard classification	*Hazard statement*
Acute Category 2	H401 - Toxic to aquatic life
Chronic Category 2	H411 - Toxic to aquatic life with long lasting effects

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical/polymer 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 notified chemical is introduced in products other than toothpaste and mouth rinse products;
- the concentration of the notified chemical exceeds or is intended to exceed 0.2% in toothpaste and mouth rinse products.

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Procter & Gamble Australia Pty Ltd (ABN: 91 008 396 245)
Level 4, 1 Innovation Road
MACQUARIE PARK NSW 2113

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

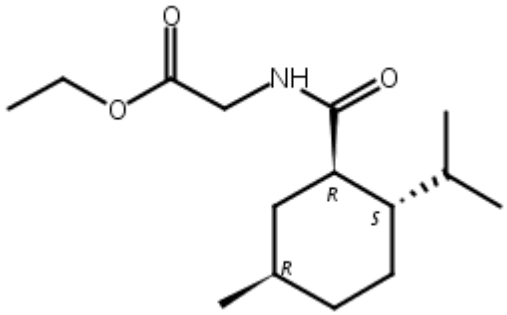
MARKETING NAME(S)
WS-5

CAS NUMBER
68489-14-5

CHEMICAL NAME
Glycine, *N*-[[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]carbonyl]-, ethyl ester

MOLECULAR FORMULA
$C_{15}H_{27}NO_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
269.38 g/mol

3. COMPOSITION

DEGREE OF PURITY
99-100%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

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

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: White to pale yellow crystal

Property	Value	Data Source/Justification
Melting Point/Freezing Point	81.2 °C	Measured
Boiling Point	148.9 °C at 0.267 kPa	Measured
Bulk Density	455 kg/m^3	Measured
Vapour Pressure	~1.04 × 10^{-3} kPa at 25 °C	Measured/estimated
Vapour Pressure	0.23 kPa at 25 °C	Measured
Water Solubility	229.1 mg/L at 20 °C	Estimated from measured octanol-water partition coefficient.
Hydrolysis as a Function of pH	Not determined	The notified polymer contains functional groups that are expected to hydrolyse very slowly in the environmental pH range (4-9).
Partition Coefficient (n-octanol/water)	log Pow = 2.73	Measured
Adsorption Coefficient	log K_{OC} = 2.8 at 25 °C	Measured
Dissociation Constant	Not determined	The notified chemical is not expected to be ionised under environmental conditions (pH 4-9)
Surface Tension	51.5 mN/m at 20 °C	Measured
Particle Size	Inhalable fraction (< 100 μm): < 50% Respirable fraction (< 10 μm): < 10%	Measured
Flash Point	Not determined	Expected to be high based on the flammability results
Flammability	Not highly flammable	Measured
Autoignition Temperature	Not determined	Expected to be high based on the flammability results
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not oxidising	Contains no functional groups that would imply oxidising properties

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured, reformulated or repackaged in Australia. The notified chemical will be imported into Australia in finished products, containing it at concentrations up to 0.2%.

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

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

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER
Symrise, Inc.
300 North Street
Teterboro NJ 07608
USA

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of formulated toothpaste and mouth rinse in tubes/containers suitable for retail sale and then transported by road for distribution to commercial warehouses and retail stores within Australia.

USE
The notified chemical will be used as a flavouring ingredient in toothpastes at concentrations up to 0.2% for adults and children 6 years old and above and mouth rinses at up to 0.01% for adults and children 6 years old and above.

OPERATION DESCRIPTION
The notified chemical will be imported into Australia as a component of toothpaste and mouth rinse products for use by the general public. Manufacture, reformulation or repackaging will not take place in Australia.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure
Transport storage and retail workers may come into contact with the notified chemical (at up to 0.2% concentration) only in the event of accidental rupture of packages.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at up to 0.2% concentration in toothpaste products and at up to 0.01% in mouth rinse products. The principal route of exposure will be oral, while accidental dermal and ocular exposure is also possible.

Data on typical use patterns of toothpaste and mouth rinse products in which the notified chemical is proposed to be used are shown in the following tables. Products containing the notified chemical will not be used by children under 6 years old. For the purposes of the exposure assessment, Australian use patterns for toothpaste and mouth rinse are assumed to be similar to those in Europe (SCCS, 2012). An adult bodyweight of 64 kg has been used for calculation purposes (enHealth, 2012). In addition, 100% systemic exposure has been assumed based on buccal and/or gastrointestinal absorption. Using these data, the total systemic exposure is estimated to be 0.0077 mg/kg bw/day of the notified chemical.

The contribution to dermal exposure from the proposed product categories is considered negligible due to the low concentrations of the notified chemical in these products and has therefore not been included in the exposure calculations.

Exposure

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Toothpaste	2,750	0.2	0.05	**0.0043**
Mouth rinse	21,620	0.01	0.1	**0.0034**

C = concentration (%); RF = retention factor; assumed brushing twice daily and using mouth rinse 4 times/day

Daily systemic exposure = (Amount × C (%) × RF x oral absorption)/body weight (64 kg)

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2500 mg/kg bw; low toxicity (SDS)
Rabbit, eye irritation	corrosive/irritating (SDS)
Rat, repeat dose oral toxicity – 90 days.	NOAEL = 75 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	mutagenic
Genotoxicity – in vitro Chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution

No data on toxicokinetics for the notified chemical was provided. For dermal absorption, molecular weights below 100 g/mol. are favourable for absorption and molecular weights above 500 g/mol. do not favour absorption (ECHA, 2017). Dermal uptake is likely to be moderate to high if the water solubility is between 100-10,000 mg/L and the log P values are between 1 and 4 (ECHA, 2017). In addition evidence of skin sensitisation or irritation increase the probability of dermal absorption occurring (ECHA, 2017). Based on the water solubility (~0.23 g/L estimated), partition coefficient (log Pow = 2.73) and low molecular weight (269.38 g/mol) of the notified chemical passage across biological membranes is expected to occur.

Acute toxicity

The notified chemical was noted in the provided SDS as being of low acute oral toxicity in rats with a LD50 of > 2,500 mg/kg bw.

Irritation and sensitisation

No data were provided on the skin irritation potential. The notified chemical is classified as irritating to eyes on the SDS provided by the notifier.

There was no data provided on the sensitisation potential of the notified chemical. However, there are no structural alerts that would imply skin sensitisation potential. The sensitisation potential of the analogous menthol isomers is considered to be low (OECD, 2003).

Repeated dose toxicity

The notified chemical was tested in a 90-day repeated oral (by gavage) dose toxicity study in rats (according to OECD Guideline 408) (test report was not available) (EFSA, 2014). The notified chemical was administered at doses of 0, 25, 75, 225 and 675 mg/kg bw/day to 10 animals/sex/dose group via gavage. Recovery groups were included for the control and high dose groups. Both sexes, showed treatment-related hepatic and renal toxicity at the highest dose (675 mg/kg bw/day). Haematological changes were observed at 225 and 675 mg/kg bw/day. A No Observed Adverse Effect Level (NOAEL) of 75 mg/kg bw/day was established.

Mutagenicity/Genotoxicity

The notified chemical was found to be non-mutagenic with or without metabolic activation in a chromosome aberration test.

In a bacterial reverse mutation test the notified chemical was found to induce a slight but statistically significant increase in the revertant counts in the *Salmonella typhimurium* strains TA1535 & TA100 and was hence considered to be mutagenic in the test. The notifier stated that the analogue cyclohexanecarboxamide, N-ethyl-5-methyl-2-(1-methylethyl)- (CAS number 39711-79-0) was not mutagenic either in the presence or absence of metabolic activation in a bacterial reverse mutation assay with *S. typhimurium* TA 98, TA 100, TA 1535, TA 1536, TA 1537 and TA 1538 as well as with yeast (test report not sighted). Menthol which shares the ring

structure as the notified chemical is not mutagenic or carcinogenic (OECD, 2003). Therefore, based on the available information the notified chemical is expected to have a low potential for mutagenicity, although it cannot be ruled out.

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

The notifier has also classified the chemical as Serious Eye Damage/Eye irritation (Category 2) in the provided SDS.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
As exposure to the notified chemical will be limited to accidental exposure of transport and storage workers, the risk to workers associated with use of the notified chemical at 0.2% concentration in toothpaste and at 0.01% in mouth rinse products is not considered to be unreasonable.

6.3.2. Public Health
The notified chemical is a serious eye irritant according to the SDS provided. The notified chemical is proposed for use at up to 0.2% concentration in toothpaste products and at up to 0.01% concentration in mouth rinse products. At these concentrations the irritant effects are not expected to occur.

The potential systemic exposure from the use of the notified chemical in toothpaste and mouth rinse was estimated to be 0.0077 mg/kg bw/day. Using a NOAEL of 75 mg/kg bw/day established from the 90-day repeat dose toxicity study on the notified chemical, the margin of exposure (MoE) was estimated to be 9,740. A MoE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure. Additionally the European Food Safety Authority concluded that the notified chemical posed “no safety concern at the estimated level of intake based on the MSDI approach” where the EU Maximised Survey-derived Daily Intake (MSDI) was estimated to be 37 µg/capita/day (EFSA, 2014).

Based on the limited available information, the risk to the public associated with the use of the notified chemical in toothpaste (at up to 0. 2% concentration) and mouth rinse products (at up to 0.01% concentration) 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 as a component of formulated toothpaste and mouth rinse products. As manufacturing and reformulation will take place overseas, no release of the notified chemical is expected to occur in Australia from these activities. Any spills during transport are expected to be contained, collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the aquatic compartment through sewers during its use in toothpaste and mouth rinse products.

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

7.1.2. Environmental Fate
Following its use in toothpaste and mouth rinse products in Australia, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. Based on a modelled

fate study the notified chemical is not expected to be readily biodegradable (BIOWIN v4.10, USA EPA 2011). Based on its estimated moderate solubility and expected low mobility in soil and sludge systems based on adsorption coefficient log Koc = 2.8 and potential surface activity, a significant proportion of the notified chemical may partition to the solid phase in sewage treatment plants (STPs). The notified chemical is not expected to bioaccumulate based on its low n-octanol/water partition coefficient (log Pow = 2.73) and potential surface activity. In surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

A proportion of the notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. The notified chemical in landfill, soil and sludge are expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.38 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 5.7 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC50 > 100 mg/L	Not harmful to aquatic invertebrates

Based on the above ecotoxicological points the notified chemical is expected to be toxic to fish. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as “Acute Category 2; Toxic to aquatic life”. Based on the acute toxicity and lack of ready biodegradability, the notified chemical has been formally classified as “Chronic Category 2; Toxic to aquatic life with long lasting effects” under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for fish. 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		
LC50 (Fish).	5.70	mg/L
Assessment Factor	500	
Mitigation Factor	1.00	
PNEC:	11.40	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.61	11.4	0.053
Q - Ocean:	0.06	11.4	0.005

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. The notified chemical is not expected to be readily biodegradable or bioaccumulative in the environment. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in toothpaste and mouth rinse products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 81.2 °C

Method	In-house method
Remarks	Capillary tube method, using photocells sensitive to changes of light transparency of the samples during the melting process indicating the temperature on the control unit.
Test Facility	Renessenz/Symrise, 2016

Boiling Point 148.9 °C at 0.267 kPa

Method	In-house method
Remarks	Boiling point capillary tubes method. The sample is heated until bubbles appearing in the boiling point capillary The boiling point will be meared when the largest increase in the number of bubbles per second.
Test Facility	Renessenz/Symrise, 2014

Bulk Density 455 kg/m^3

Method	In-house method
Remarks	Compressibility Index method (Carr index). Measuring the Tap density (652 kg/m^3) using 24.11 g of the test substance and finding a Tap volume of 37.0 ml (Initial volume of the sample was 53.0 ml). The compressibility index was 30.19%.
Test Facility	Micromeritics Analytical Services, 2012

Vapour Pressure ~1.04 × 10^{-3} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure
Remarks	The vapour pressure of the test item was estimated from its boiling point either at normal atmospheric pressure or reduced pressure. New Substances Notification Regulations (NSNR) and Guidelines (Handbook of Chemical Property Estimation Methods) recognises the determination of the vapour pressure from alternative test protocols or from calculation or estimation methods.
Test Facility	Intertek/Symrise

Vapour Pressure 0.23 kPa at 25 °C

Method	OECD TG 104 Vapour Pressure.
Remarks	Vapour Pressure Balance Method
Test Facility	Envigo CRS Limited (2017)

Partition Coefficient (n-octanol/water) log Pow = 2.73

Method	OECD TG 117 Partition Coefficient (n-octanol/water) EC Council Regulation No 440/2008 A.8 Partition Coefficient
Remarks	HPLC Method. The mobile phase was adjusted to neutral pH to ensure the test material was tested in its non-ionised form.
Test Facility	Safepharm Laboratories Limited (2005a)

Adsorption/Desorption log K_{oc} = 2.8 at 25 °C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (K_{oc}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
Remarks	Determined by using high performance liquid chromatography (HPLC)
Test Facility	Envigo CRS Limited (2017)

Particle Size Inhalable fraction (< 100 µm): < 50%
Respirable fraction (< 10 µm): < 10%

Method Particle Insight - Particle Shape Analyzer

Range (μm)	*Volume (%)*
40.4	10
59.7	25
113.7	50
235.0	75
371.7	90

Remarks Calculated for the equivalent circular area diameter
Test Facility Renessenz, LLC/Symrise (2012)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks Determined using a test mould and an ignition source
Test Facility Envigo CRS Limited (2017)

Oxidizing Properties Not oxidising

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks Determined by measuring the potential for a material to increase the burning rate of a combustible substance
Test Facility Envigo CRS Limited (2017)

Surface Tension 51.5 mN/m at 20 °C

Method OECD TG 115 Surface Tension of Aqueous Solutions
EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks Concentration: 90% saturated solution (~70 mg/L)
Test Facility Envigo CRS Limited (2017)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure & Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, *E. coli*: WP2uvrA$^-$
Metabolic Activation System	Phenobarbitone and β-naphthoflavone
Concentration Range in Main Test	a) With metabolic activation: 50 to 5,000 µg/plate b) Without metabolic activation: 50 to 5000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	No significant protocol deviations A third confirmatory experiment was run using *S. typhimurium* strains TA1535 and TA100, in the absence of metabolic activation at concentrations of 2,000 – 5,000 µg/plate, using both the plate incorporation and pre-incubation metods.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5,000		≥ 3000	positive
Test 2		> 5,000	≥ 3000	negative
Test 3		> 5,000	≥ 4,000	positive
Present				
Test 1	> 5,000		≥ 5,000	negative
Test 2		> 5,000	≥ 5,000	negative

Remarks - Results	There was a slight but statistically significant increase in the revertant counts in the *S. typhimurium* strains TA1535 & TA100 at doses of 1,500 and 5,000 µg/plate, in the absence of metabolic activation in test 1. This slight increase, in the absence of metabolic activation. was also present in test 2 but did not reach statistical significance. In the confirmatory test (test 3) statistically significant increases were seen at all the tested doses. The 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 mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories Limited (2005b)

B.2. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 476 In vitro Mammalian Cell Gene Mutation Test. EC Directive 2000/32/EC B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test.
Species/Strain	Mouse
Cell Type/Cell Line	Lymphoma / L5178Y TK +/- 3.7.2c

Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	DMSO
Remarks - Method	No significant protocol deviations. Positive controls used were: Ethylmethanesulphonate (EMS) in the absence of metabolic activation, and Cyclophosphamide (CP).in the presence of metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Harvest Time*
Absent				
Test 1	0*, 10.51, 21.02, 42.03*, 84.06*, 168.13*, 336.25*, 504.38*, 672.5*	4 h	2 days	10-14 days
Test 2	0*, 10.51*, 21.02*, 42.03*, 84.06*, 168.13*, 252.2*, 336.25*, 504.38*	24 h	2 days	10-14 days
Present				
Test 1	0*, 42.03, 84.06*, 168.13*, 336.25*, 504.38*, 672.5*, 1008.75*, 1345	4 h	2 days	10-14 days
Test 2	0*, 42.03*, 84.06*, 168.13*, 336.25*, 504.38*, 672.5*, 1008.75, 1345	4 h	2 days	10-14 days

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 672.5	≥ 504.38	> 672.5	negative
Test 2	≥ 336.25	≥ 336.25	> 504.38	negative
Present				
Test 1	≥ 1345	≥ 1008.75	≥ 1345	negative
Test 2		≥ 504.38	> 1345	negative

Remarks - Results	The maximum concentration level used was limited by the test substance induced cytotoxicity. The test substance did not induce any statistically significant or concentration related increases in the mutant frequency at any concentration level either in the presence or absence of metabolic activation in both tests. The positive control and vehicle control gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to L5178Y TK +/- mouse lymphoma cell line treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm Laboratories Limited (2006)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test –Semi-static.
Species	*Oncorhynchus mykiss*
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks – Method	The stock solution was prepared by dissolving 1100 mg in 11 litres of dechlorinated tap water and stirred for 24 hours. Any undissolved material was removed by filtration through 0.2 µm Sartorius Sartopore filter to produce a 100 mg/L stock solution.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual**		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	<LOQ[§]	7	0	0	0	0	0
1.0	0.89	7	0	0	0	0	0
3.2	2.55	7	0	0	0	0	0
10	9.71	7	0	7	7	7	7
32	31.0	7	0	7	7	7	7
100	108	7	7	7	7	7	7

*Measured concentrations of notified chemical at time=0 hours.
[§]LOQ=limit of quantification

LC50	5.7 mg/L (95% CI 4.1-7.8) at 96 hours
NOEC	3.2 mg/L at 96 hours
Remarks – Results	Measured concentrations were 76-110% of nominal concentrations at time 0, 24, 72 and 96 hours. The results were based on the nominal concentrations.
CONCLUSION	The notified chemical is considered to be toxic to fish.
TEST FACILITY	Envigo Research Limited (2015)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks - Method	The stock solution was prepared by dissolving 1100 mg in 11 litres of dechlorinated tap water and stirred for 24 hours. Any undissolved material was removed by filtration through 0.2 µm Sartorius Sartopore filter to produce a 100 mg/L stock solution.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	<LOQ*	20	0	0
100	106§	20	0	0

*LOQ=limit of quantification

§ Mean value of measured concentrations at 0 and 48 hours

EC50	>100 mg/L at 48 hours
NOEC (or LOEC)	100 mg/L mg/L at 48 hours
Remarks - Results	The results from the positive control with potassium dichromate were within normal range. There was no immobilization in 20 daphnids exposed to a test concentration of 100 mg/L for a period of 48 hours.
CONCLUSION	The notified chemical is not considered to be harmful to aquatic invertebrates.
TEST FACILITY	Envigo Research Limited (2015)

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