File No: STD/1649

September 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis(1-methyldecyl)-

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

TABLE OF CONTENTS

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
STD/1649	Henkel Australia Pty Ltd	1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis(1-methyldecyl)-	Yes	≤ 15 tonnes per annum	Fragrance ingredient for laundry and household cleaning products

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Skin sensitiser (Category 1B)	H317 – May cause an allergic skin reaction

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 low hazard and reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin sensitiser (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 processes:
  - Enclosed, automated process, where possible
  - Adequate 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 during reformulation processes:
  - Avoid skin contact

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

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

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

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a fragrance ingredient for laundry and household cleaning products, or is likely to change significantly;

- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

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

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year)

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: absorption/desorption, dissociation constant and acute dermal toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
ECHA (2010), Korea (2011) and USA (2012)

2. IDENTITY OF CHEMICAL

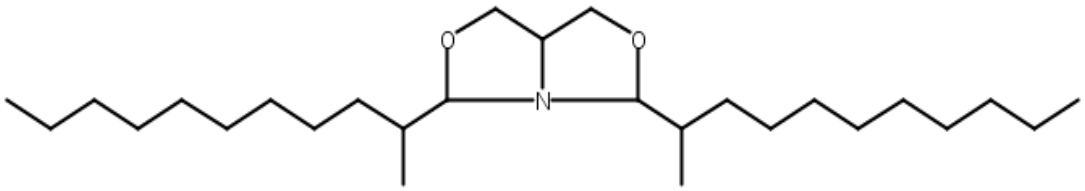
MARKETING NAME
Sa190

CAS NUMBER
1001161-63-2

CHEMICAL NAME
1*H*,3*H*,5*H*-Oxazolo[3,4-*c*]oxazole, dihydro-3,5-bis(1-methyldecyl)-

MOLECULAR FORMULA
$C_{27}H_{53}NO_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
423.72 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 98%

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: yellowish liquid with crystalline solid

Property	Value	Data Source/Justification
Melting Point	-51 °C – 32 °C	Measured
Boiling Point	320 °C at 101.3 kPa	Measured
Density	908.1 kg/m^3 at 20 °C	Measured
Vapour Pressure	≤ 9.9 × 10^{-6} kPa at 20 °C	Measured
Water Solubility	> 7 µg/L at 20 °C	Estimated
Hydrolysis as a Function of pH	pH 4 = Unstable pH 9 = Unstable pH 7 = ½ life 108 hours at 20 °C = ½ life 38 hours at 50 °C = ½ life 5 hours at 70 °C	Measured
Partition Coefficient (n-octanol/water)	log Pow > 5.7 at 40 °C	Measured
Adsorption/Desorption	Not determined	Unstable in water
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	199 °C	Measured
Flammability	Not flammable in contact with water	Measured
Autoignition Temperature	350 °C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	Measured

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia mostly as a component of fragrance oil at ≤ 12% concentration. The notified chemical may also be imported into Australia as a component of finished consumer products such as laundry and household cleaning products at ≤ 0.1% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	5	5	10	15	15

PORT OF ENTRY
Sydney and Brisbane

IDENTITY OF RECIPIENTS
Pax Australia Pty Ltd
Jalco Household and Fabric Care

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of finished products at ≤ 0.1% concentration packed in containers suitable for retail sale or as fragrance oil at ≤ 12% concentration in 200 L drums and 1,000 L intermediate bulk containers (IBCs). Finished consumer products containing the notified chemical 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 chemical will be used as a fragrance ingredient in laundry and household cleaning products (such as detergents, fabric softeners and hard surface cleaners) at ≤ 0.1% concentration.

OPERATION DESCRIPTION
Reformulation of the fragrance oil containing the notified chemical at ≤ 12% 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 ≤ 0.1% concentration) will be used by consumers and professionals such as 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 warehouse	None	Incidental
Mixing	4	10
Drum handling	4	10
Drum cleaning/washing	4	10
Maintenance	5	2
Quality control	4	10
Packaging	4	10

EXPOSURE DETAILS

Transport and storage
Transport, storage and warehouse workers may come into contact with the notified chemical at ≤ 12% concentration in fragrance oil formulation or at ≤ 0.1% concentration (in final formulated products), only in the event of accidental rupture of containers. If such an event occurs, workers may be exposed through dermal, ocular or perhaps inhalation exposure. Exposure will be minimised through the use of personal protective equipment (PPE) including protective coveralls, impervious gloves and eye protection, as stated by the notifier.

Reformulation
During reformulation dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at ≤ 12% concentration may occur while handling of drums, during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. It is expected that exposure will be minimised

through the use of mechanical ventilation and/or enclosed systems, and workers wearing PPE such as protective clothing, eye protection and impervious gloves.

End-use
Exposure to the notified chemical in end-use products (at ≤ 0.1% concentration) may occur in professions where the services provided involve in the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure are 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 repeated exposure of the public to the notified chemical at ≤ 0.1% concentration through the use of a wide range of laundry and household cleaning products. The main route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables based on European use information provided in various literatures (ACI, 2010; RIFM, 2010). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 100% was assumed for the notified chemical for calculation purposes. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Household products (Indirect dermal exposure - from wearing clothes):

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.1	0.95	10	0.0034
Fabric softener	90	0.1	0.95	10	0.0013
Total					**0.0048**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.1	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.1	1980	0.009	0.01	0.03	0.0003
All-purpose cleaner	1	0.1	1980	1	0.01	0.007	0.0022
Total							**0.0024**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical at the maximum intended concentrations specified by the notifier in various product types. This would result in a combined internal dose of 0.0072 mg/kg bw/day for the notified chemical.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Skin irritation (*in vitro*) – RHE* test method	non-irritating
Eye irritation (*in vitro*) – HET-CAM**	non-irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation (EC3 = 34.4%)
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	clastogenic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non clastogenic
Rat, reproductive and developmental toxicity – dose range finding study	NOAEL = 1,000 mg/kg bw/day

* Reconstructed Human *Epidermis*
**HET-CAM: Hen's Egg Test – Chorio-allantoic Membrane

Toxicokinetics
Given the low molecular weight (423.72 g/mol) the notified chemical may be absorbed across the respiratory or gastrointestinal tract. Based on its expected low water solubility and high partition coefficient (calculated Pow = > 5.7) the notified chemical has a reasonably high lipophilicity, and hence percutaneous absorption is limited.

Acute toxicity
The notified chemical is of low acute oral toxicity based on a study conducted in rats.

No studies were submitted for acute dermal or inhalation toxicity. No signs of systemic toxicity were observed in a mouse local lymph node assay (LLNA).

Irritation and sensitisation
The notified chemical is considered as non-irritating to skin and eyes based on *in vitro* studies.

The notified chemical was determined to be a skin sensitiser in a mouse LLNA with stimulation indices of 2.11, 4.47 and 4.80 at 25%, 50% and 100% concentrations, respectively. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 34.4%, indicating the notified chemical as a weak skin sensitiser.

Repeated dose toxicity
In a 28-day repeated dose oral toxicity study in rats (5/sex/dose), the notified chemical was administered daily by gavage at dose levels of 100, 300, and 1,000 mg/kg bw/day. Yellow mucoid fluid was observed in the pericardium of one single male of each of the low, mid and high dose groups. As no associated histopathological findings in the heart of these animals or any other signs of toxicity were observed, this finding was not considered as adverse by the study authors. An increase in absolute kidney weight was noted in male animals of all dose groups. In contrast, in female animals a lower absolute kidney weight was found in the high dose group. In the absence of histopathological findings this was not considered adverse by the study authors. The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 1,000 mg/kg bw/day based on the absence of toxicologically significant effects at any dose tested. The information available is not sufficient to relate the fluid accumulation in the pericardium in 1/5 treated males in all dose groups was treatment related or not.

Mutagenicity/Genotoxicity
The notified chemical was non-mutagenic in a bacterial reverse mutation assay and in an *in vitro* mammalian cell gene mutation test in Chinese hamster V79 cells. In an *in vitro* chromosome aberration test in Chinese hamster V79 cells the notified chemical was found to be clastogenic in the presence of metabolic activation. However, the notified chemical was found to be not clastogenic in an *in vivo* mouse erythrocyte micronucleus assay via intraperitoneal injection.

Based on the weight of evidence from these studies, the notified chemical is not expected to be genotoxic.

Reproductive and developmental toxicity
In a dose-range finding combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats (3/sex/dose), the notified chemical was administered daily by gavage at dose levels of 100, 300 and 1,000 mg/kg bw/day. An abnormal dark cranial pole of one kidney in a male and dilated kidney in

another male of the high dose group was observed at necropsy in offspring. The study authors indicated these findings are considered to be incidental and not treatment related. The NOAEL for parental and reproductive and developmental toxicity was established by the study authors as 1,000 mg/kg bw/day based on no adverse effects observed at any dose levels tested.

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

Hazard classification	*Hazard statement*
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is a weak skin sensitiser.

Reformulation
During reformulation, workers may be exposed to the notified chemical introduced at ≤ 12% concentration. At this concentration, workers may be at risk of sensitisation. According to the notifier engineering controls such as enclosed automated process and local ventilation will be implemented where possible and appropriate PPE (coveralls, impervious gloves, eye protection and respiratory protection) will be used to limit worker exposure to the notified chemical. Therefore provided the control measures are in place to minimise worker exposure, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve use of household products in the cleaning industry may be exposed to the notified chemical at ≤ 0.1% concentration. No skin sensitisation effects are expected at the very low concentration in the end-use products. Professional cleaners may use gloves to minimise repeated exposure, and good hygiene practices are expected to be in place. The risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers using various products containing the notified chemical.

6.3.2. Public Health
Members of the public will experience widespread and frequent exposure to the notified chemical at ≤ 0.1% concentration through daily use of laundry and household cleaning products. The main route of exposure is expected to be dermal, while ocular and inhalational exposures are also possible, particularly if products are applied by spray.

The notified chemical is a weak skin sensitiser. At the proposed low use concentration in laundry and household cleaning products the risk of sensitisation is not expected.

Based on the available information, systemic toxicity from use of the notified chemical at ≤ 0.1% concentration in laundry and household products is not expected.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.1% concentration in laundry and household cleaning 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 as a component of a fragrance formulation for reformulation into finished laundry and household cleaning products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the product

containing the notified chemical is 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 a fully enclosed environment. Therefore, significant release of the notified chemical 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 and use. Wastes containing the notified chemical 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 30 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 chemical is expected to be released to sewer across Australia as a result of its use in laundry and household cleaning products. A small proportion of the notified chemical is 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 chemical may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified chemical 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 chemical is expected to enter the sewer system through its use as a component of laundry and household cleaning products before potential release to surface waters nationwide. The notified chemical is hydrolytically unstable, in environmental conditions, but is not considered to be readily biodegradable (56.8% in 29 days). Whilst the notified chemical is not readily biodegradable, it is considered ultimately biodegradable and is not expected to bioaccumulate. For details of the environmental fate studies, refer to Appendix C.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when 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 chemical has low water solubility and hydrolyses rapidly and is predicted to be hydrophobic. Therefore, in the waste water treatment processes in the sewage treatment plant (STP), most of the notified chemical is expected to degrade or partition to sludge or to suspended solids where it will be removed for disposal to landfill. In landfill the notified chemical is 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 calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported uses in laundry and household cleaning products, it is conservatively assumed that 100% of the notified chemical will be released to sewer on a nationwide basis over 365 days per year. It is also assumed that under a worst-case scenario there is no removal of the notified chemical during STP processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	15,000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	15,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	41.10	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0	%
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	

Dilution Factor - Ocean	10.0	
PEC - River:	8.43	µg/L
PEC - Ocean:	0.84	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 chemical 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 8.42 µg/L may potentially result in a soil concentration of approximately 0.056 mg/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 0.28 mg/kg and 0.56 mg/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	LC50 > 110 mg/L (WAF)	Not harmful to fish up to the limit of its water solubility
Daphnia Toxicity	EC50 > 12.6 µg/L	Not toxic to aquatic invertebrates up to the limit of its water solubility
Algal Toxicity	EC50 > 7 µg/L	Not harmful to algae up to the limit of its water solubility

Based on the above ecotoxicological data, the notified chemical is not expected to be harmful to aquatic life up to the limit of its water solubility. Therefore, the notified chemical is 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 chemical is not considered to be harmful to aquatic life up to the limit of its solubility in water.

7.3. Environmental Risk Assessment

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point -51 °C – 32 °C

Method EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks Determined using differential scanning calorimetry. The study authors state that the test substance showed a start of melting at -51 °C of a subcomponent 1, followed by a crystallisation (possibly with a subcomponent 2) and the end of melting at + 32 °C.
Test Facility Henkel (2009a)

Boiling Point 320 °C at 102.1 kPa

Method EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks Determined using differential scanning calorimetry
Test Facility Henkel (2009b)

Density 908.1 kg/m^3 at 20 °C

Method EC Council Regulation No 440/2008 A.3 Relative Density
Remarks Determined using oscillating densitimeter method
Test Facility Henkel (2009c)

Vapour Pressure $\leq 9.9 \times 10^{-6}$ kPa at 20 °C

Method EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks Determined using differential scanning calorimetry
Test Facility Henkel (2009d)

Water Solubility > 7µg/L (estimated)

Method EU test method L383 A/54-62 (EU A.6).
Remarks Column Elution Method. A preliminary study indicated that the water solubility of the test substance was below 10 mg/L. Therefore, the column elution method was used. However, the test substance decomposed in the column and hence the study was aborted. However, during the algal toxicity study it was estimated that the water solubility is > 7µg/L.
Test Facility Henkel (2009e)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH
EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ hours*
4	50	Unstable
7	20	108
7	50	38
7	70	5
9	50	Unstable

Remarks The temperature dependence of the rate constant at pH 4 and pH 9 could not be determined. Due to immediate hydrolysis; the test substance could not be detected. The pH values of the solutions before and after the hydrolysis indicated no significant change observable in any of the test solutions. The test substance was found to be hydrolytically unstable under all pH conditions.
Test Facility Henkel (2014)

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

Method	EU test method L383 A/63-73 (EU A. 8).
Remarks	The reference item triphenylamine has a log Pow value of 5.7. The test procedure is only applicable within log Pow values from - 2 to +6. The preliminary test indicated the log Pow for the test substance to be > 5.7 based on HPLC Method.
Test Facility	Henkel (2009f)

Flash Point 199 °C

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Determined using Pensky-Martins flash point apparatus
Test Facility	Henkel (2009g)

Flammability Not flammable in contact with water

Method	EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water)
Test Facility	Henkel (2009h)

Autoignition Temperature 350 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Test Facility	Henkel (2009i)

Explosive Properties Not explosive

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	The notified chemical was not thermally sensitive or mechanical sensitive with respect to shock.
Test Facility	Henkel (2010)

Oxidizing Properties Not oxidising

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Test Facility	Henkel (2009j)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical (> 98% purity)

METHOD: OECD TG 423 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	3M/3F	2,000	0/6

- LD50: > 2,000 mg/kg bw
- Signs of Toxicity: No signs of toxicity were observed.
- Effects in Organs: No abnormalities were observed at necroscopy.
- Remarks - Results: Slightly ruffled fur was observed on two males on day 1 of the observation.

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

TEST FACILITY: Harlan (2009a)

B.2. Irritation – skin (*in vitro*)

TEST SUBSTANCE: Notified chemical (> 98% purity)

METHOD: OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method
- Vehicle: Nil
- Remarks - Method: Positive and negative controls were run in parallel with the test substance:
  - Negative control: deionised water
  - Positive control: 5% sodium lauryl sulphate

  The MTT [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue] assay was used to determine cell viability.

  No protocol deviations.

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.8241	100.0	7.2
Test substance	0.8571	104.0	6.5
Positive control	0.1331	16.2	1.2

OD = optical density; SD = standard deviation

- Remarks - Results: The test substance was shown not to directly reduce MTT.

  The relative mean tissue viability for the test substance as compared to the negative control was 104.0%. Given that the relative mean tissue viability for the test substance was > 50%, it is considered a non-irritant.

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

CONCLUSION The notified chemical is not classified as a skin irritant according to GHS criteria.

TEST FACILITY Harlan (2009b)

B.3. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical (> 98% purity)

METHOD INVITTOX Protocol No 47: HET-CAM Test

Remarks - Method Chorioallantoic membranes of six fertilised eggs (incubated for 8 days) were treated with 300 µL of the notified chemical. The notified chemical was applied directly on to 50% of the chorioallantoic membrane. The irritancy or the corrosive potential of the notified chemical was determined by the presence of damages (haemorrhage, coagulation and lysis of the blood vessel) in the chorioallantoic membrane blood vessels during observation period of 300 seconds.

Positive controls: 1% sodium dodecyl sulfate (SDS) and 0.1 mol/L sodium hydroxide (NaOH)

Negative control: 0.9% (w/v) physiological sodium chloride

RESULTS

Test material	*Mean time until haemorrhage (seconds)*	*Mean time until lysis (seconds)*	*Mean time until coagulation (seconds)*	*Mean irritancy index*
Negative control	301	301	301	0.00
Test substance	301	301	301	0.00
Positive control (NaOH)	14	52	17	19.12
Positive control (SDS)	15	80	301	9.92

Remarks - Results No signs of irritation were observed in any chorioallantoic membranes treated with notified chemical and the negative control.

The positive controls induced severe irritation of the blood vessels (i.e. mean irritancy index ≥ 9)

CONCLUSION The notified chemical is non-irritating to the eye under the conditions of the test.

TEST FACILITY Harlan (2009c)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical (> 98% purity)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain Mouse/CBA/Ca

Vehicle Acetone:olive oil (4:1)

Preliminary study Yes

Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.

Remarks - Method No significant protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*

Test Substance			
0 (vehicle control)	4F	539.0	-
25	4F	1137.1	2.11
50	4F	2407.8	4.47
100	4F	2588.9	4.80
Positive Control			
0	Not stated	727.6	-
5	Not stated	1303.6	1.79
10	Not stated	1518.4	2.09
25	Not stated	4976.6	6.84

EC3 34.4%

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

The stimulation indices were 2.11, 4.47 and 4.80 at 25%, 50% and 100% concentrations, respectively, indicating a sensitising response. The stimulation index was calculated to be 34.4%.

The positive control behaved as expected, confirming the validity of the test system.

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

TEST FACILITY Harlan (2009d)

B.5. Repeat dose toxicity

TEST SUBSTANCE Notified chemical (100% purity)

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents

Species/Strain Wistar rats, Crl:WI(Han)

Route of Administration Oral – gavage

Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: Nil

Vehicle Corn oil

Remarks - Method No clinical observations were performed in the first 2 weeks of the study. Females were not fasted (overnight) prior to obtaining blood samples.

No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
control	5M/5F	0	0/10
low dose	5M/5F	100	1/10
mid dose	5M/5F	300	0/10
high dose	5M/5F	1,000	0/10

Mortality and Time to Death

No treatment related mortalities occurred during the study. A female from low dose was euthanised in *extremis* on day 19 of the study. Pericardial inflammation, pleural inflammation and mediastinal inflammation at the thymus were observed at necropsy. Study authors states this effect was considered as incidental (gavage error) and not related to treatment.

Clinical Observations

There were no clinical signs of toxicity. There was no effect on body weight, food consumption or in any of the parameters of the functional observation battery.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No effects were noted on clinical chemistry, haematological or urinary parameters.

Effects in Organs
The thoracic cavity of the female animal that was euthanised *in extremis* was filled with white fluid and the heart and thymus were abnormally dark.

Yellow mucoid fluid was observed in the pericardium of one single male in each of the low, mid and high dose groups. As no associated histopathological findings in the heart of these animals or any other signs of toxicity were observed, this finding was not considered adverse by the study authors. However, the study authors also states a relation to the test substance could not be excluded.

An increase in absolute kidney weight was noted in male animals of the low (17% above controls), mid (13% above controls) and high (19% above controls) dose groups. In contrast, in female animals a lower absolute kidney weight was found in the high dose group (19% below controls). In the absence of histopathological findings this was not considered adverse by the study authors.

An increase in absolute liver weight was noted in male animals of the low (8% above controls), mid (10% above controls) and high (11% above controls) dose groups. In contrast, in female animals lower absolute liver weight was found in the low (11% lower than controls) and high (17% lower than controls) dose groups. In the absence of histopathological findings this was not considered adverse by the study authors.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established by study authors as 1,000 mg/kg bw/day in this study, based on the absence of toxicologically significant effects at any dose tested.

TEST FACILITY	BSL (2018a)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical (> 98% purity)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test
Species/Strain	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	<u>Test 1 (plate incorporation method):</u> a) With or without metabolic activation: 3, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate <u>Test 2 (pre-incubation method):</u> b) With or without metabolic activation: 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate
Vehicle	Dimethylformamide (DMF)
Remarks - Method	A preliminary test at a concentration range of 3.0 – 5,000 µg/plate (with or without metabolic activation) was conducted on TA98, TA100, TA1535, TA1537 and WP2uvrA. As no toxicity was observed up to 5,000 µg/plate, the preliminary test is reported as Test 1. Vehicle and positive control studies were conducted in parallel with the main study. Negative control: DMF Positive control: With metabolic activation: 2-aminoanthracene (TA100 and TA1537), 4-nitro-o-phenylene-diamine (TA98 and TA1537) and methyl methane sulfonate (WP2uvrA). Without metabolic activation: sodium azide (TA1535 and TA100), No protocol deviations.

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	> 5,000	≥ 2,500	Negative
Test 2		> 5,000	> 5,000	Negative
Present				
Test 1	> 5,000	> 5,000	≥ 2,500	Negative
Test 2		> 5,000	> 5,000	Negative

Remarks - Results

No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with the test substance at any dose level, in the presence or absence of metabolic activation. There were also no dose dependent increases in mutation rates.

The positive controls gave satisfactory responses, confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

RCC (2008)

B.7. Genotoxicity – *in vitro* Mammalian Cell Gene Mutation Test

TEST SUBSTANCE

Notified chemical (> 98% purity)

METHOD

OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test

Species/Strain: Chinese hamster

Cell Type/Cell Line: V79

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

Vehicle: Ethanol

Remarks - Method: Negative control: ethanol

Positive control: without metabolic activation: ethylmethanesulfonate

with metabolic activation: 7,12- dimethylbenz(a)anthracer

In a preliminary test, V79 cells were treated with the notified chemical at 16.5 to 4237.0 μg/mL for 4 hours with or without metabolic activation. An additional study without metabolic activation was conducted for 20 hours.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	16.5*, 33.0*, 66.1*, 132.4*, 264.8*, 529.6*, 1059.3*, 2118.6*, 3177.9* and 4237.0*	4 h	24 h
Test 2	16.5*, 33.0*, 66.1*, 132.4*, 264.8*, 529.6*, 1059.3*, 2118.6*, 3177.9* and 4237.0*	20 h	24 h
Present			
Test 1	16.5*, 33.0*, 66.1*, 132.4*, 264.8*, 529.6*, 1059.3*, 2118.6*, 3177.9* and 4237.0*	4 h	24 h
Test 2	10.6*, 21.2*, 42.4*, 105.9*, 211.9*, 423.7*, 847.4*, 1694.9*, 2966.0* and 4237.0*	4 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 4237.0	> 4237.0	≥ 529.6	Negative
Test 2	> 4237.0	> 4237.0	≥ 529.6	Negative
Present				
Test 1	> 4237.0	> 4237.0	≥ 529.6	Negative
Test 2		> 4237.0	≥ 423.7	Negative

Remarks - Results

An increased value of the mutation frequency relative to the solvent control was noted in Test 1 with metabolic activation at 33, 67.8, 529.6, 2118.5, 3177.7 and 4237 µg/mL, and in Test 2, without metabolic activation at 16.5, 33, 266.9, 529.6, 1059 and 4237 µg/mL and with metabolic activation at 847.4 µg/mL. However, this increase was judged as being biologically irrelevant since the threshold (three times the mutation frequency) was not exceeded and there was no dose dependant trend.

The positive controls behaved as expected, confirming the validity of the test system.

CONCLUSION

The notified chemical was not mutagenic to Chinese hamster V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY

BSL (2012a)

B.8. Genotoxicity – *in vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE

Notified chemical (> 98% purity)

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test

Species/Strain: *Chinese hamster*

Cell Type/Cell Line: V79

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

Vehicle: Ethanol

Remarks - Method: Negative control: ethanol

Positive control: without metabolic activation: ethylmethanesulfonate

with metabolic activation: cyclophosphamide

In a preliminary test, V79 cells were treated with the notified chemical at 8.5 to 4237.0 µg/mL for 4 hours both with and without metabolic activation. An additional study without metabolic activation was conducted for 20 hours.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	13.4, 42.4*, 67.8, 133.9, 423.7, 1059.3, 2118.6*, and 4237.0*	4 h	20 h
Test 2	4.2, 13.4, 42.4*, 67.8, 133.9, 423.7, 1059.3, 2118.6*, and 4237.0*	20 h	20 h
Present			
Test 1	13.4*, 42.4, 67.8, 133.9, 423.7*, 1059.3, 2118.6*, and 4237.0*	4 h	20 h
Test 2	169.5*, 339.0, 847.4, 1694.9, 2542.3, 3389.68*, and 4237.0*	4 h	20 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 4237.0	> 4237.0	≥ 2118.5	Negative
Test 2		> 4237.0	≥ 2118.5	Negative
Present				
Test 1	> 4237.0	> 4237.0	≥ 2118.5	Positive
Test 2		> 4237.0	≥ 3389.6	Positive

Remarks - Results

In Test 1 and Test 2 without metabolic activation, no biologically relevant increase in structural chromosomal aberrations was observed.

In Test 1, with metabolic activation, an increase (4.5%) above the historical negative control (0.0% - 4.0%) in structural chromosomal aberrations was observed at a concentration of 13.4 µg/mL.

In Test 2, with metabolic activation, an increase in structural chromosomal aberrations above the historical negative control was observed at concentrations of 169.5 (6.8% increase) and 3389.6 (5.0% increase) µg/mL.

In both experiments with and without metabolic activation no biologically relevant increase in the frequencies of polyploid cells was found after treatment with the test substance as compared to the controls.

The positive controls behaved as expected, confirming the validity of the test system.

CONCLUSION

The notified chemical was clastogenic to Chinese hamster V79 cells with metabolic activation treated *in vitro* under the conditions of the test.

TEST FACILITY

BSL (2012b)

B.9. Genotoxicity – *in vivo* Mammalian Erythrocyte Micronucleus Test

TEST SUBSTANCE

Notified chemical (> 98% purity)

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test (July 1997)

Species/Strain

Mouse/NMRI Charles River

Route of Administration

Intraperitoneal

Vehicle

Cottonseed oil

Remarks - Method

A preliminary dose range finding study was conducted on three males and three females at a dose level of 2,000 mg/kg bw. All treated animals showed mild toxic effects including reduction of spontaneous activity, constricted abdomen, piloerection, bradykinesia and half eyelid closure. All signs of toxicity were resolved at the 48 hour observation.

No unscheduled mortalities were observed during the study.

No protocol deviations.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5M/5F	-	NA*
II (low dose)	5M/5F	400	NA*
III (mid dose)	5M/5F	1,000	NA*
IV (high dose)	5M/5F	2,000	NA*
V (positive control, CP)	5M/5F	40	NA*

CP=cyclophosphamide
*peripheral blood was sampled at 44 hours and 68 hours after treatment

RESULTS

Doses Producing Toxicity	All animals treated with the high dose showed mild toxic effects including reduction of spontaneous activity, swollenness in movement (bradykinesia) and half eyelid closure. All signs of toxicity were resolved at the 24 hour observation. No clinical signs of toxicity were observed in the low and mid dose treated animals, vehicle control or positive control animals during the study period.
Genotoxic Effects	The test substance induced no statistically significant increases in micronucleated, polychromatic erythrocytes (PCEs) at the sampling time.
Remarks - Results	The incidence of micronucleated immature erythrocytes for the high dose group had increased compared to the negative control. This increase was, however, not statistically significant and within the historical negative control values. Therefore this increase is not considered biologically relevant. The positive control performed as expected, confirming the validity of the test system.

CONCLUSION The notified chemical was not clastogenic under the conditions of this *in vivo* mouse micronucleus test.

TEST FACILITY Eurofins (2015)

B.10. Reproductive and developmental toxicity

TEST SUBSTANCE Notified chemical (100% purity)

METHOD Dose –range finding study. OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

Species/Strain	Rat/Wistar (Crl:WI(Han))
Route of Administration	Oral – gavage
Exposure Information	Exposure days: males: 28 days including during 14 days of premating and maximum of 14 days of mating females: during 14 days of premating and maximum of 14 days of mating, up to post-natal day 3 Dose regimen: 7 days per week
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	3M/3F	0	0/6
Low dose	3M/3F	100	0/6
Mid dose	3M/3F	300	0/6
High dose	3M/3F	1,000	0/6

Mortality and Time to Death
No unscheduled mortalities occurred during the study period for parental animals.

Two male pups (out of 38 pups) born to a mid-dose group female and one male and one female pup (out of 42 pups) born to a high-dose female were found dead on postnatal day 0. No histopathology examinations were conducted on these dead pups. This was not considered to be test substance-related by the study authors.

Effects on Dams

A 100% copulation index, fertility index and delivery index were recorded for both control and treatment groups. A slight reduction in viability index was observed for the mid- and high-dose group pups (95.6%) compared to the control group (100%). The study authors indicated that this finding was not considered to be toxicologically significant as the value is within the historical control data.

At necropsy, slight but not dose dependently higher ovary weights (20% increase compared to control) and uterus weights (44% increase compared to control) were observed in animals of the high dose. This was not assumed to be toxicologically relevant by the study authors.

Effects on Foetus

Total number of live pups born to animals exposed to mid- (46.2% increase compared to control) and high-dose (67.6% increase compared to control) groups was comparatively higher than the control group and this was due to the fact that higher number of treatment related implantation sites but not corpora lutea was recorded for the mid- (39.3% increase compared to control) and high-dose (53.6% increase compared to control) groups. Furthermore, higher pre-implantation loss in control animals (22.3%), when compared to the high-dose group (1.96%) was observed. Lower post-implantation loss was observed in all the treatment groups (5% to 6%) compared to the control group (13%). The study authors indicated that these values were within the normal range of historical control data.

Body weights of the mid- and high-dose pups were higher than the control group on postnatal day 0 (19.6% and 27.2% higher than the control group for mid- and high-dose groups, respectively) and on postnatal day 4 (20.7% and 22.8% higher than the control group for mid- and high-dose group animals, respectively). The increased pup body weight observed on postnatal days 0 and 4 were considered not to be test substance related, based on the absence of any clear dose-response and statistical significance.

At necroscopy an abnormal dark cranial pole of one kidney in a male and dilated kidney in another male of the high dose group was observed. The study authors indicated these findings are considered to be incidental and not treatment related.

Remarks - Results

There were no mortalities. All clinical signs were within the expected range for animals of this strain and age. No treatment-related statistically significant differences were observed on mean body weights, body weight changes and food consumption.

There were no toxic effects on parental male and reproductive performance as well as pup related parameters.

CONCLUSION

The NOAEL for parental and reproductive and developmental toxicity was established as 1,000 mg/kg bw/day in this study.

TEST FACILITY BSL (2018b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution (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	2.1	4	17.6
7	3.3	7	52.4
11	7.7	11	69.4
23	43.2	23	78.3
29	56.8	29	80.2

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound reached the threshold level of 60% by 11 days and attained 80% degradation by 29 days. Therefore, the test indicates the suitability of the inoculums. No degradation was observed, but hydrolysis of the notified chemical would not lead to CO_2, evolution . The toxicity control attained 53.2% degradation up to day 23 thereby confirming that the notified chemical was not toxic to the sewage treatment micro-organisms used in the study. After 29 days the toxicity control had attained 61.4% degradation. The test material attained 56.8% 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 ready biodegradable.
TEST FACILITY	LAUS (2009a)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical (> 98.1%)
METHOD	OECD TG 203 Acute Toxicity for Fish -Static
Species	Rare minnow (*Gobiocypris rarus*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	165 - 177 mg $CaCO_3$/L

Analytical Monitoring	GC-FID
Remarks – Method	A range finding test was conducted using five fish per test concentrations of 1, 10 and 100 mg/L, as well as a control. No mortalities were observed in any of the test concentrations. On the basis of the range finding test, a limit test was conducted. The notified chemical was added directly to the test medium, stirred for 24 hours and allow to settle for 1 hour. Three replicates of seven fish per treatment were exposed to the limit concentration of 110 mg/L, a control and a positive control (single treatments of 10 fish using potassium dichromate between 100 and 500 mg/L). 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	21	0
110 (WAF)	0.417	21	0

WAF = Water Accommodated Fraction
LOQ not recorded

LC50	> 0.417 mg/L (measured, WAF) at 96 hours
NOEC	≥ 0.417 mg/L (measured, WAF) at 96 hours
Remarks – Results	Dissolved Oxygen (DO) values varied from 73% and 94%. All validity criteria were met. The mean measured concentration was 0.417 mg/L. Although the concentration decreased with time, 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 and the mean measured concentration. 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 harmful to fish up to the limits of its water solubility.

TEST FACILITY PEAPC (2016)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical (> 98.1%)

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

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Methanol (1 mL/L)
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 16 mg/L of the notified chemical in methanol was prepared. This was mixed with dilution water at a ratio of 22.2 µg/L to 25 mL resulting in a theoretical concentration of 14.2 µg/L and added to the test aquaria at an exchange rate of once per 109.7 minutes. Five replicates of four daphnia per treatment were exposed to the test concentration of 14.2 µg/L, (above the estimated water solubility limit of 7 µg/L in the test media), a control and a positive control (single treatments of five daphnia using potassium dichromate between 0.5 and 3.0 mg/L). The concentration of the notified chemical was measured at the start of the study and daily

thereafter, until study termination.

RESULTS

Concentration µg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
Control (0)	< 2	20	0	1
Solvent Control (0)	N.D,	20	0	1
7	12.6	20	2	2

N.D. = Not determined

LC50	> 12.6 µg/L at 24 hours > 12.6 µ g/L at 48 hours
NOEC (or LOEC)	≥ 12.6 µg/L at 48 hours
Remarks - Results	Dissolved Oxygen (DO) values varied from 7.6 to 8.7 mg/L. All validity criteria were met. The temperature was within a range of 22.0 to 26.5 °C and therefore higher than stated in the guidelines. However, this did not appear to effect the results of the study. The measured concentrations were above the estimated water solubility of 7 µg/L for the first 24 hours. The mean measured concentration was 12.6 µg/L and this value was used in the determination of the effects on daphnia. The 24 hour LC50 of the positive control was 1.6 mg/L, which was within the accepted range. No abnormal behaviour was observed in any of the treatments.
CONCLUSION	The notified chemical is not harmful 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 (> 98.1%)
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	Nominal: 7 µg/L Actual: < 2 - 7.4 µg/L
Auxiliary Solvent	Methanol
Water Hardness	Not determined
Analytical Monitoring	
Remarks - Method	On the basis of low water solubility, a limit test was conducted. A stock solution containing 8.75 g/L of the notified chemical in methanol was diluted in methanol resulting in a solution of 87.5 mg/L. This solution was used to prepare the treatments. Six replicates containing ~ 1×10^4 cells/mL were exposed to a test concentration of nominally 7 µg/L, a control and a positive control (triplicate treatments using potassium dichromate between 0.04 and 1.6 mg/L). The concentration of the notified chemical was measured at the start and end of the study.

RESULTS

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

> 7	≥7	> 7	≥7

Remarks - Results	Normal growth of algae was observed in all treatments (excluding the positive control). The cell concentration in the control grew by a factor of 114; the mean coefficient of variation of daily growth rates was 35%; and the coefficient of variation of average maxima was 2%. Therefore all validity criteria were satisfied. The measured concentration was 7 µg/L at the beginning of the study and could not be detected at study termination. As the notified chemical could not be detected at study termination, the nominal concentration was used in the determination of the effects on alga. The 24 hour LC50 of the positive control was 0.84 mg/L, which was within the accepted range.
CONCLUSION	The notified chemical is not harmful to algae up to the limits of its water solubility.
TEST FACILITY	LAUS (2009c)

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