File No.: LTD/2115

February 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Genadvance Repair

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

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

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

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/2115	Clariant (Australia) Pty Ltd	Genadvance Repair	No	≤ 5 tonnes per annum	Component of hair care products

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification

Based on the available information, the notified polymer is not recommended for classification 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*
Chronic Category 1	H410 - Very toxic to aquatic life with long lasting effects

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

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

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified polymer itself. However, these should be selected on the basis of all ingredients in the formulation, noting that the formulation may be classified because of hazardous impurities.

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

Emergency procedures

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

Disposal

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified 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 polymer has a number-average molecular weight of less than 1000 g/mol;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the polymer has changed from a component of hair care products, or is likely to change significantly;
  - the amount of polymer being introduced has increased, or is likely to increase, significantly;
  - the polymer has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the polymer 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 polymer 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)
Clariant (Australia) Pty Ltd (ABN: 30 069 435 552)
Level 3, 3 Acacia Place
296-324 Ferntree Gully Road
NOTTING HILL VIC 3168

NOTIFICATION CATEGORY
Limited: Synthetic polymer with Mn ≥ 1,000 g/mol

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details exempt from publication include: chemical name, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, polymer constituents, residual monomers, impurities, additives/adjuvants, import volume and analogue identity.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for density, vapour pressure, adsorption/desorption, dissociation constant, flash point, flammability, autoignition temperature, explosive properties and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Genadvance Repair

OTHER NAME(S)
Quaternium-98 (INCI name)
Ethoxylated multi-chain quaternary ammonium salt

MOLECULAR WEIGHT
Number average molecular weight (Mn) is > 1,000 g/mol.

ANALYTICAL DATA
Reference IR and GPC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	*Value*	*Data Source/Justification*
Melting Point/Freezing Point	-12.9 – -3.1 °C at 101.3 kPa	Measured
Boiling Point	257 ± 9 °C at 101.4 kPa	Measured
Density	ca. 1,021 kg/m^3 at 20 °C	SDS
Vapour Pressure	ca. < 1 × 10^{-3} kPa at 25 °C	SDS
Water Solubility	> 1000 g/L at 23 °C	Measured

Property	*Value*	*Data Source/Justification*
Hydrolysis as a Function of pH	$t_{1/2}$ > 5 days at pH 4-9	Measured
Partition Coefficient (n-octanol/water)	log Pow = -0.4 at 20 °C	Measured. Expected to partition to the interface between octanol and water based on its surfactant properties
Adsorption/Desorption	log K_{oc} = 2.82 & 4.04 at 23.4°C (soil) log K_{oc} = 2.83 & 4.25 at 23.4°C (sewage)	Measured. Expected to accumulate at phase boundaries based on its surfactant properties and cationic functionality
Dissociation Constant	Not determined	The notified polymer is a salt and will be ionised under environmental conditions
Flash Point	ca. 100 °C	SDS
Flammability	Not determined	Not expected to be highly flammable based on flash point
Autoignition Temperature	Not determined	Not expected to undergo autoignition
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties

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

Reactivity
The notified polymer 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 polymer is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

The notified polymer has a calculated flash point of 100 ºC which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the notified polymer may be considered as a Class C2 combustible liquid if the polymer has a fire point below the boiling point.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified polymer will not be manufactured in Australia. It will be imported into Australia in neat form for reformulation into hair care products. The notified polymer will also be imported in finished hair care products at ≤ 3% concentration.

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

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

PORT OF ENTRY
Throughout Australia

TRANSPORTATION AND PACKAGING
The notified polymer (neat) will be imported in 180 kg drums. Finished hair care products containing the notified polymer may commonly be imported in small retail size containers for consumers, inside shipping containers. The imported neat notified polymer and finished products containing the notified polymer will be transported by road or rail.

USE
The notified polymer is a hair conditioning agent. It can be used in a range of hair care products including rinse-off and leave-on conditioners, shampoos, hair oils and other similar end use products. In finished consumer products the maximum proposed use concentration of the notified polymer is ≤ 3%.

OPERATION DESCRIPTION
The notified polymer will not be manufactured in Australia. Reformulation of the notified polymer into end use hair care products will occur within Australia.

Reformulation
At the reformulation sites, procedures for incorporating the notified polymer into end use products will likely vary depending on the nature of the formulated products and may involve both automated and manual transfer steps. In general, it is expected that the notified polymer will be weighed and added to the mixing tank where mixing with additional additives will occur to form finished hair care products. Subsequently, automated filling of the reformulated products into containers of various sizes (up to 2 L) will occur. The blending and filling operations are expected to be typically automated with enclosed systems and adequate ventilation. During the reformation process, samples of products containing the notified polymer will be taken for quality assurance (QA) purposes.

End use
Consumers and professionals such as hairdressers will use the finished hair care products containing the notified polymer at concentrations of ≤ 3%. Depending on the nature of the products, applications may be by hand or through the use of applicators.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and Storage	4	12
Reformulation	8	12
Quality assurance	3	12
Packaging	8	12
Retail	4	12
Professional end users	8	200

EXPOSURE DETAILS

Transport and storage
Transport and storage workers are not expected to be exposed to the notified polymer except in the unlikely event of an accident, as the notified polymer and the products containing the notified polymer will be sealed in containers during transport and storage.

Reformulation and packaging
During reformulation operations, dermal and ocular exposure of workers to the notified polymer in neat form is possible when weighing and transferring of the notified polymer from imported containers into blending tanks. Inhalation of the notified polymer is not expected unless the polymer becomes airborne. The notifier stated that PPE, such as coveralls, gloves and eye protection will be used when handling the notified polymer. During filling operations, potential exposure of workers to the notified polymer in finished hair care formulations (at concentrations of ≤ 3%) will likely be through dermal or ocular routes. The exposure is expected to be minimised by the use of automated/enclosed systems and appropriate PPE for workers.

QA staff will wear laboratory coats, gloves and safety glasses to minimise exposure to the notified polymer in samples during quality control processes.

End-use
Exposure to the notified polymer in end use products (at concentrations of ≤ 3%) may occur in professions where the services provided involve the application of finished hair care products to clients (e.g. hair dressers or workers in hairdressing salons). The principal route of exposure will be dermal with the potential for ocular exposure to occur from splashes or wiping of eyes/face. Professional users (for instance hair dressers) may use some PPE (such as gloves) to minimise repeated exposure but this may not occur in all workplaces. Exposure of such workers is expected to be of a similar or lesser extent when compared with the exposure experienced by consumers using various hair care products containing the notified polymer.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified polymer (at concentrations of ≤ 3%) through the use of a range of hair care products. The main route of exposure will be dermal, while ocular and oral exposures are also possible. Inhalation exposure may also be possible if the notified polymer is used in hair care products that are applied by spray.

6.2. Human Health Effects Assessment
No toxicity data were submitted for the notified polymer. The results from toxicological investigations conducted on an analogue are summarised in the following table. For details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Skin irritation – rabbit*	non-irritating
Eye irritation – rabbit*	non-irritating
Skin sensitisation – guinea pig, Magnusson and Kligman*	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation*	non mutagenic
Genotoxicity – *in vitro* mammalian gene mutation test*	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test*	non genotoxic

* The test substance was an analogue which is structurally similar to the notified polymer (identity is exempt information).

Toxicokinetics
No information on the toxicokinetics, metabolism and distribution of the notified polymer was submitted. Based on the high molecular weight of the notified polymer (Mn > 1,000 g/mol) and low partition coefficient (-0.4 at 20-25 °C), it is not expected to be readily absorbed across biological membranes.

Acute Toxicity
No acute toxicity data are available.

Irritation and Sensitisation
No information on irritation and sensitisation for the notified polymer was submitted. An analogue was found to be non-irritating to the skin and eyes in studies in rabbits. Irritation scores were 0 at 1-hour, 24-hour, 48-hour and 72-hour observations in both studies. The analogue was also found to be non-sensitising in a guinea pig maximisation test. Therefore, the notified polymer is expected to be non-irritating to the skin and eyes and is not expected to be a sensitiser.

Repeated Dose Toxicity
No repeated dose toxicity data were available, but limited dermal absorption is expected due to the high molecular weight of the notified polymer.

Mutagenicity/Genotoxicity
No information on mutagenicity/genotoxicity for the notified polymer was submitted. An analogue was found to be non-mutagenic in a bacterial reverse mutation assay and in an *in vitro* mammalian cell gene mutation test using Chinese hamster ovary cells. The analogue was also found to be non-genotoxic in an *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes. Based on the results for the analogue polymer, the notified polymer is not expected to be genotoxic or mutagenic.

Health Hazard Classification
Based on the available information, the notified chemical/polymer is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

Based on the information available, the notified polymer is not expected to cause local effects, and is not expected to be readily absorbed across biological membranes, therefore also limiting the possibility of systemic effects.

6.3.1. Occupational Health and Safety

Reformulation

Reformulation workers may come into contact with the notified polymer at various concentrations including the neat form. The main route of exposure is expected to be dermal but accidental ocular exposure is also possible. Inhalation exposure is unlikely unless aerosols are formed during reformulation activities. Safe work practices, engineering controls and use of PPE, including eye protection, chemical resistant gloves, and protective clothing would further reduce the exposure to workers.

End use

Beauty care professionals and salon workers will handle end use products containing the notified polymer at concentrations of ≤ 3%. As certain protective measures including PPE may be used by these professionals, the risk to the workers is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis.

Provided control measures are in place to limit exposure, the risk to the health of reformulation workers is not considered to be unreasonable.

6.3.2. Public Health

Members of the public may experience repeated exposure to the notified polymer through the use of finished hair care products (containing the notified polymer at concentrations of ≤ 3). The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Although the systemic effects (acute and repeated dose toxicity) data for the notified polymer are not available, significant systemic exposure is not expected from use of the notified polymer in finished hair care products given the high molecular weight of the notified polymer limiting dermal absorption. Therefore, adverse effects are not expected from the use of finished hair care products containing the notified polymer.

Therefore, based on the information available, the risk to the public associated with use of the notified polymer at the proposed concentrations of ≤ 3% in finished hair care 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 polymer will not be manufactured in Australia. It will be imported into Australia (> 95% concentration) as a surfactant for reformulation and/or in finished cosmetic hair care products (up to approximately 3%). Release of the notified polymer to the environment is unlikely except in the event of a transport accident or an accidental spill during handling. Accidental spills of formulated products containing the notified polymer are expected to be physically contained and then absorbed into inert material. The absorbed notified polymer is expected to be disposed of to landfill.

The reformulation process will involve both automated and manual transfer of the raw material containing the notified polymer into blending vessels, followed by blending operations that are expected to be highly automated and occur within a fully enclosed environment. The process will be followed by automated filling of the finished products into end-use containers of various sizes. Wastes containing the notified polymer generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. Wastes may be collected and released to sewers, or disposed of to landfill in accordance with state and local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the annual import volume of the notified polymer is expected to be released to the aquatic compartment through sewers during its use in various hair cosmetic products such as rinse-off and leave-on conditioners, shampoos, hair treatments, masks, and hair oils.

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated by the notifier that 3% of the import volume of the notified polymer may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified polymer 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

No environmental fate data were submitted for the notified polymer. The results of a submitted biodegradability study of an analogue suggest that the notified polymer is considered to be not readily biodegradable (24-25% in 28 days). For the details of the environmental fate study refer to Appendix C.

Following its use in cosmetic formulations, the majority of the notified polymer is expected to enter the sewer system, before potential release to surface waters nationwide. Due to its cationic functional group and surface activity, a significant amount of the notified polymer is expected to sorb to sludge in STPs. The sludge containing the notified polymer residues may be sent to landfill or applied to soils for land remediation. The notified polymer released to surface waters is expected to partition to suspended solids and organic matter, or to disperse and degrade. Consequently, the notified polymer is not expected to be significantly bioavailable. The potential for the notified polymer to bioaccumulate is low based on its surfactant properties. The notified polymer is expected to ultimately degrade biotically and abiotically to form water and oxides of carbon, nitrogen and sulfur.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the notified polymer being washed into the sewer. The predicted environmental concentration (PEC) has been calculated based on the realistic scenario with 100% release of the notified polymer into sewer systems nationwide over 365 days per annum. The extent to which the notified polymer is removed from the effluent in STP processes is based on the information regarding its behaviour in the STP. Cationic polymers with a NAMW > 1000 are expected to have 90% removal in STPs (US EPA 2013). The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5000	kg/year
Proportion expected to be released to sewer	100	%
Annual quantity of chemical released to sewer	5000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	13.70	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	90	%
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC – River:	0.28	µg/L
PEC – Ocean:	0.03	µg/L

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 25.28 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified polymer may approximate 0.169 mg/kg in applied soil. This assumes that degradation of the notified polymer occurs in the soil within 1 year from application. Assuming accumulation of the notified polymer in soil for 5 and 10 years under repeated biosolids application, the concentration of notified polymer in the applied soil in 5 and 10 years may approximate 0.845 mg/kg and 1.69 mg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity*	48 hr EC50 = 1.07 mg/L	Toxic to aquatic invertebrates
Algal Toxicity*	72 hr EC50 = 0.865 mg/L	Very toxic to algae

*Study conducted on an analogue of the notified polymer

Based on the above ecotoxicological endpoints for the analogue, the notified polymer is expected to be very toxic to aquatic organisms. Therefore, the notified polymer is classified as "Acute Category 1; Very toxic to aquatic life" according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009). The notified polymer is not readily biodegradable and is not expected to bioaccumulate. Therefore, the notified polymer is formally classified as "Chronic Category 1; Very toxic to aquatic life with long lasting effects" under the GHS for its long-term hazard.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) of the notified polymer was calculated using the most sensitive ecotoxicity endpoint provided (72 h algae EC50 = 0.87 mg/L). An assessment factor of 500 was used as acute aquatic endpoints covering two trophic levels were available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
ErC50 (Algae)	0.87	mg/L
Assessment Factor	500	
Mitigation Factor	1.00	
PNEC	1.73	µg/L

7.3. Environmental Risk Assessment

The risk quotient is calculated as the ratio of the PEC to PNEC:

Risk Assessment	PEC (µg/L)	PNEC (µg/L)	Q
Q – River	0.28	1.73	**0.162**
Q – Ocean	0.03	1.73	**0.016**

The risk quotient has been calculated based on the assumption of release of 100% of the notified polymer into the sewers. Since the Q value determined was less than 1 for both river and ocean compartments the notified polymer is unlikely to reach ecotoxicologically significant concentrations based on the proposed annual importation and use pattern. The potential for the notified polymer to bioaccumulate is low based on its surfactant properties. Being a cationic surfactant, a significant amount of the notified polymer is expected to sorb to sludge in STPs which is expected be sent to landfill or applied to soils. The notified polymer is not readily biodegradable however is expected to ultimately degrade biotically and abiotically to form water and oxides of carbon, nitrogen and sulfur. On the basis of the PEC/PNEC ratio, the notified polymer is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -12.9 – -3.1 °C at 101.3 kPa

Method OECD TG 102 Melting Point/Melting Range
Remarks Determined by differential scanning calorimetry
Test Facility Clariant (2019a)

Boiling Point 257 ± 9 °C at 101.4 kPa

Method OECD TG 103 Boiling Point
Remarks Determined by differential scanning calorimetry
Test Facility Clariant (2019b)

Water Solubility > 1000 g/L at 20 °C

Method OECD TG 105 Water Solubility
EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks Flask Method
Test Facility Clariant (2018a)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ days*
4	50	> 5
7	50	> 5
9	50	> 5

Remarks GPC Method
Test Facility Clariant (2018b)

Partition Coefficient (n-octanol/water) log Pow = -0.4 at 23 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water)
Remarks Shake Flask Method
Test Facility Clariant (2018c)

Adsorption/Desorption log K_{oc} = 2.82 & 4.04 (Signal 1 & 2) at 23.4 °C Soil
log K_{oc} = 2.83 & 4.25 (Signal 1 & 2) at 23.4 °C Sewage Sludge

Method OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
Remarks HPLC-DAD
Test Facility NL (2019)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Skin Irritation – Rabbit

TEST SUBSTANCE	Analogue 1 (identity is exempt information)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations
RESULTS	
Remarks – Results	The irritation scores were 0 at the 1-hour, 24-hour, 48-hour and 72-hour observations.
CONCLUSION	The test substance is non-irritating to the skin.
TEST FACILITY	Bioneeds (2017a)

B.2. Eye Irritation – Rabbit

TEST SUBSTANCE	Analogue 1 (identity is exempt information)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 hours
Remarks – Method	No significant protocol deviations
RESULTS	
Remarks – Results	The irritation scores were 0 at the 1-hour, 24-hour, 48-hour and 72-hour observations.
CONCLUSION	The test substance is non-irritating to the eye.
TEST FACILITY	Bioneeds (2017b)

B.3. Skin Sensitisation – Guinea Pig Maximisation Test

TEST SUBSTANCE	Analogue 1 (identity is exempt information)
METHOD	OECD TG 406 Skin Sensitisation – Magnusson and Kligman
Species/Strain	Guinea pig/Hartley
PRELIMINARY STUDY	Maximum non-irritating concentration: Intradermal: 5% Topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 10 M Control Group: 5 M
Vehicle	Distilled water
Positive Control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 2-mercapto benzothiazole.
INDUCTION PHASE	Induction concentration: Intradermal: 5% Topical: 100%
Signs of Irritation	Following intradermal injection very slight erythema and oedema were seen in both treated and vehicle control animals.
CHALLENGE PHASE	

Challenge	Topical: 100% (14 days after induction completed)
Remarks – Method	No significant protocol deviations

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: Challenge*	
		24 h	*48 h*
Test Group	100%	0/10	0/10
Vehicle Control Group	100%	0/5	0/5

Remarks – Results	No clinical signs or gross pathological changes were noted in treated or control animals. All animals showed normal body weight gain. None of the test or control animals showed any skin reactions during the challenge phase.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.

TEST FACILITY Bioneeds (2018a)

B.4. Genotoxicity – Bacteria

TEST SUBSTANCE Analogue 1 (identity is exempt information)

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

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA (pKM101),
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 0.02-2 µL/plate b) Without metabolic activation: 0.02-2 µL/plate
Vehicle	Distilled water
Remarks – Method	The dose selection for the main test was based on the cytotoxicity results in the preliminary test carried out at 1 – 5 µL/plate. Positive controls: With metabolic activation: 2-aminoanthracene Without metabolic activation: 2-nitrofluorene (TA98), 4-nitroquinoline 1-oxide (WP2uvrA), 9-aminoacridine (TA1537); sodium azide (TA100, TA1535)

RESULTS

Metabolic Activation	*Test Substance Concentration (µL/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 3	≥ 2	> 2	negative
Test 2		≥ 2	> 2	negative
Present				
Test 1	≥ 3	≥ 2	> 2	negative
Test 2		≥ 2	> 2	negative

Remarks – Results	No significant increases in the frequency of revertant colonies were noted for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation. The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION	The test substance was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Bioneeds (2017c)

B.5. Genotoxicity – *In Vitro* Mammalian Cell Gene Mutation Test

TEST SUBSTANCE	Analogue 1 (identity is exempt information)
METHOD	OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test
Species/Strain	Chinese hamster ovary (CHO)
Cell Type/Cell Line	AA8
Metabolic Activation System	S9 mix from β-naphthoflavone/phenobarbitone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks – Method	The dose selection for the main test was based on the toxicity results in the preliminary tests carried out at 0.0078 – 2 mg/mL. Vehicle and positive controls (benzo(a)pyrene and 4-nitroquinoline 1-oxide) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 0.00195*, 0.0039*, 0.0078*, 0.0156*	3.6 h	9 d
Present			
Test 1	0*, 0.00195*, 0.0039*, 0.0078*, 0.0156*	3.6 h	9 d

*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	≥ 0.0078	≥ 0.0156	> 0.0156	negative
Present				
Test 1	≥ 0.0078	≥ 0.0156	> 0.0156	negative

Remarks – Results	The test substance did not induce any statistically significant increases in the mutant frequency at any tested concentration in each exposure group, with or without metabolic activation.
CONCLUSION	The test substance was not mutagenic to Chinese hamster ovary (CHO) AA8 cells treated *in vitro* under the conditions of the test.
TEST FACILITY	Bioneeds (2018b)

B.6. Genotoxicity – *In Vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE	Analogue 1 (identity is exempt information)
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Human
Cell Type/Cell Line	Peripheral blood lymphocytes
Metabolic Activation System	S9 mix from β-naphthoflavone/phenobarbitone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks – Method	The dose selection for the main test was based on the toxicity results in the preliminary test carried out at 0.125 – 2 mg/mL.

Vehicle and positive controls (mitomycin-C and cyclophosphamide monohydrate) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 0.0625*, 0.125*, 0.25*	3 – 6 h	20 – 24 h
Test 2	0*, 0.0625*, 0.125*, 0.25*	20 – 24 h	20 – 24 h
Present			
Test 1	0*, 0.0625*, 0.125*, 0.25*	3 – 6 h	20 – 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	≥ 0.5	> 0.25	> 0.25	negative
Test 2	≥ 0.5	> 0.25	> 0.25	negative
Present				
Test 1	≥ 0.5	> 0.25	> 0.25	negative

Remarks – Results

In the main tests, no statistically significant increases in the frequency of cells with structural or numerical chromosome aberrations were noted in the presence or absence of metabolic activation.

The results of the positive controls confirmed the validity of the test system.

CONCLUSION

The test substance was not clastogenic to human peripheral blood lymphocyte cells treated *in vitro* under the conditions of the test.

TEST FACILITY

Bioneeds (2017d)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Analogue 2 (identity is exempt information)
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test
Inoculum	Activated Sewage Sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	None
Remarks – Method	The study was carried out in accordance with the test guidelines and GLP. The test was run in parallel to controls and the reference material, sodium benzoate.

RESULTS

Test Substance		*Sodium Benzoate*	
Day	*% Degradation**	*Day*	*% Degradation*
6	11	6	71
13	17	13	90
21	21	21	94
28	27	28	97

*Mean of two replicates

Remarks – Results	The study met all validity criteria. The standard reference material reached more than ≥ 60% degradation within 6 days. The difference between replicate values of CO_2 production was < 20%; the CO_2 production in the control vessels did not exceed 40 mg/L and the toxicity control reached ≥ 25% degradation within 6 days. The biodegradation of the reference item was not inhibited by the test item in the toxicity control. The test substance attained 27% degradation after 28 days and therefore cannot be considered to be readily biodegradable.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	NL (2016a)

C.2.1. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE	Analogue 2 (identity is exempt information)
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	180 mg $CaCO_3$/L
Analytical Monitoring	TOC
Remarks – Method	The study was carried out in accordance with the test guidelines and GLP where no deviations were recorded. Following preliminary range-finding tests, 20 daphnids were exposed to the test item at nominal concentrations up to 8 mg/L. A 24 h positive control was run with potassium dichromate.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
0.250	ND	20	0	0
0.500	ND	20	0	2
1.00	ND	20	3	8
2.00	ND	20	15	20
4.00	ND	20	16	20
8.00	ND	20	20	20

EC50 1.07 mg/L at 48 hours
NOEC 0.250 mg/L at 48 hours

Remarks – Results The validity criteria of the test were met. No daphnids in the control group showed immobilisation or signs of disease. The dissolved O_2 at the end of exposure was ≥ 7.94 mg/L, pH was between 7.27-8.94 and the temperature range was 19-20 °C. The EC50 value was calculated by sigmoidal dose-response regression. The positive control result (EC50 = 1.01 mg/L) was within the acceptable range.

CONCLUSION The test substance is toxic to aquatic invertebrates.

TEST FACILITY NL (2016b)

C.2.2. Algal Growth Inhibition Test

TEST SUBSTANCE Analogue 2 (identity is exempt information)

METHOD OECD TG 201 Alga, Growth Inhibition Test
Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 0.100 – 5.72 mg/L
Actual: Not determined
Auxiliary Solvent None
Water Hardness 240 mg $CaCO_3$/L
Analytical Monitoring TOC
Remarks – Method The study was carried out in accordance with the test guidelines and GLP where no deviations were recorded. Following preliminary range-finding tests, algae were exposed to the test item at nominal concentrations up to 5.72 mg/L. A positive control was run with potassium dichromate.

RESULTS

Biomass		*Growth*	
EyC50 mg/L at 72 h	*NOEC mg/L*	*ErC50 mg/L at 72 h*	*NOEC mg/L*
0.590	0.275	0.865	0.275

Remarks – Results All validity criteria for the test were satisfied. The mean cell density in the control increased 361 times after 72 hours (required: ≥ 16). The mean coefficient of variation for section specific growth rate for the control culture was 12.1% (required: ≤ 35%) and the average specific growth rate for the control was 0.95% (required: < 7%). The EC50s were calculated by sigmoidal dose-response regression. The NOECs were determined by calculation of statistically significant differences of growth rates and yield. The statistical tests conducted were the Shapiro-Wilk's test, Levene's test, monotonicity tested by trend analysis and contrast and the

	Welsh t-test after Bonferroni. The positive control results (ErC50 = 0.46 mg/L and EyC50 = 0.317 mg/L) were within the acceptable range.
CONCLUSION	The test substance is very toxic to algae.
TEST FACILITY	NL (2016c)

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