File No: LTD/2035

July 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Chemical in LTFA

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:

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/2035	HP PPS Australia Pty Ltd	Chemical in LTFA	ND*	≤ 1 tonne per annum	Component of industrial 3D printing agent.

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during printing and sandblasting operations:
  - Enclosed, automated processes 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 printing and sandblasting operations:
  - Avoid inhalation of generated dust.

- 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 printing and sandblasting operations:
  - Respiratory protection

  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(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the notified chemical is introduced in a powder form other than the described purpose-designed sealed printing cartridge.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from component of industrial 3D printing agent, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
HP PPS Australia Pty Ltd (ABN: 16 603 480 628)
Level 5, 1 Homebush Drive
RHODES NSW 2138

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, use details, and manufacture/import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH, partition coefficient, absorption/desorption, dissociation constant, flash point and reactivity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
Canada NDSL (2010).
European Union REACH (2017).
Japan.
South Korea ECL (2014), AREC (2016).
United States TSCA (2017).
Taiwan TSCI (2015).

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
LTFA.

MOLECULAR WEIGHT
< 500 g/mol (for the empirical formula).

ANALYTICAL DATA
Reference FTIR spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 99%

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: Blue powder.

Property	Value	Data Source/Justification
Melting Point	> 450 °C	Measured.
Boiling Point	Not determined.	Not required as no melting of the test substance was identified at > 300 °C.
Density	6,740 kg/m^3 at 20 °C	Measured.
Vapour Pressure	6.3 × 10^{-7} kPa at 25 °C	Measured.
Water Solubility	≤ 6.14 x 10^{-3} g/L at 20 °C	Measured.
Hydrolysis as a Function of pH	Not determined	The notified chemical is an inorganic solid.
Partition Coefficient (n-octanol/water)	Not determined	The notified chemical is an inorganic solid.
Surface Tension	72.2 mN/m	Measured.
Adsorption/Desorption	Not determined	Based on its low solubility in water, the notified chemical is expected to settle to sediment and sludge.
Dissociation Constant	Not determined	The notified chemical is an inorganic solid, with no dissociable functionality.
Particle Size	Inhalable fraction (< 100 μm): 78.4% Thoracic fraction (< 10 μm): ≤ 0.87% Respirable fraction (< 5 μm): < 0.1%	Measured.
Flash Point	Not determined.	Not expected to form flammable vapour.
Flammability	Not highly flammable.	Measured. Particle size data was not provided in the study paper.
Flammability	Non-flammable.	Measured. Not flammable in contact with water. No signs of spontaneous ignition.
Pyrophoric properties	Non-pyrophoric.	Measured. No signs of spontaneous ignition.
Autoignition Temperature	> 400 °C	Measured.
Explosive Properties	Predicted negative.	Estimated
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 be imported as a component of a substance used for 3D printing.

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

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

PORT OF ENTRY
Melbourne and Sydney.

IDENTITY OF MANUFACTURER/RECIPIENTS
HP PPS Australia Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as a component of a formulation/solution at ≤ 10% concentration in a purpose-designed sealed printing cartridge with 500 mL capacity.

USE
The notified chemical will be used in digital 3D printing of plastic parts.

OPERATION DESCRIPTION
Reformulation
No reformulation, repackaging or manufacture of the notified chemical will take place within Australia.

End use
Printer operators will manually remove the cartridge (containing the notified chemical at ≤ 10% concentration) from the cardboard packaging and install it in the printer. The printing process is automated and occurs within the enclosed printer apparatus. Fusing agent (containing the notified chemical) is applied to polymer particles (printing material) and following exposure to heat, the fusing agent fuses the polymer particles together and forms a polymer matrix containing the notified chemical bound within it. Completed printed items may be sandblasted. This is expected to occur within an enclosed chamber. However, sanding items by hand may also occur. Completed printed items may also be painted.

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 workers	2	12
Operators	8	300
Service technicians	2 - 4	12 - 24

EXPOSURE DETAILS
Transport and storage
No exposure is anticipated to occur, unless in an accident where the containers are breached and the material is spilt.

Formulation of end products
Printing operations will be largely enclosed and automated. Workers may be exposed (ocular, dermal and inhalation) to the notified chemical at a concentration of ≤ 10% when loading and replacing cartridges and during routine maintenance and repair. Dermal and ocular exposure to workers is expected to be minimised through the stated use by the notifier of personal protective equipment (PPE) such as coveralls, goggles, dust mask and impervious gloves. Inhalation exposure is not expected unless aerosols are formed as the notified chemical exhibits a low vapour pressure at ambient temperatures. Inhalation exposure to aerosols of the notified chemical is expected to be minimised through the use of local exhaust ventilation and enclosed processes.

Sandblasting operations are expected to be largely enclosed and automated. However, sanding of completed items by hand may also occur. The notified chemical is expected to be bound within a polymer matrix and not available for exposure. Workers may be exposed (dermal and ocular) to the notified chemical at a concentration of ≤ 10% when loading and unloading printed items and during routine maintenance and repair of sandblasting machines, or when handling items as part of sanding by hand. Exposure to workers is expected to be minimised through the stated use by the notifier of personal protective equipment (PPE) such as coveralls, goggles, dust mask and impervious gloves. Inhalation exposure is not expected unless dust is formed through the sanding process. Inhalation exposure to particles containing the matrix-bound notified chemical is expected to be minimised through the use of local exhaust ventilation and enclosed processes.

Painting operations are expected to occur by hand. However, the notified chemical is expected to be bound within a polymer matrix and not available for exposure.

6.1.2. Public Exposure

The finished printed products containing the notified chemical at ≤ 10% concentration are intended for industrial use and will not be available to the public. Once the ink is cured and dried, the notified polymer will be part of an inert matrix and will not be available for exposure.

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 > 2,500 mg/kg bw; low toxicity
Skin irritation (*in vitro*) - EPISKIN™	non-irritating.
Eye irritation (*in vitro*) – EpiOcular™ EIT (OCL-200)	non-irritating.
Eye irritation (*in vitro*) – BCOP	no prediction can be made.
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation.
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics, metabolism and distribution

No information on the toxicokinetics of the notified chemical was provided. The notified chemical has low water solubility (< 6.14 mg/L) and is a crystalline inorganic polymer with a particle size of > 5 µm (99.9%) and therefore dermal absorption is not expected.

Acute toxicity

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

Irritation

The notified chemical was non-irritating to the skin and is considered to be non-irritating to the eye based on *in vitro* studies conducted on a human epidermis model (EpiSkin Reconstructed Human Epidermis Model) and Reconstructed Human Cornea-like Epithelium (RhCE) Model (EpiOcular EIT), respectively.

Sensitisation

The notified chemical did not show evidence of skin sensitisation in a local lymph node assay (LLNA) tested at a maximum concentration of 50%.

Repeated dose toxicity

No repeated dose toxicity studies were provided. Systemic exposure to the notified chemical is not expected based on its low water solubility and particle size. The notified chemical is not expected to be significantly cytotoxic based on cell viability measurements taken as part of determining if the notified chemical could be classified as a skin irritant.

Mutagenicity/Genotoxicity

The notified chemical was not mutagenic in a bacterial reverse mutation assay. No other genotoxicity data are available.

Health hazard classification

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

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

The notified chemical is expected to be of low acute oral toxicity based on a study conducted in rats. The notified chemical is not expected to be irritating to the skin or eyes based on *in vitro* studies, or a sensitiser based on an LLNA study in mice.

No toxicity information following inhalation exposure to the notified chemical was provided. The notified chemical is subject to a Final Significant New Use Rule (SNUR) promulgated under Section 5(a)(2) of TSCA (EPA has determined that manufacturing, processing or use of this substance may cause serious health effects). This decision was based on concerns for lung overloading and lung cancer as observed in test data on analogous crystalline respirable, poorly soluble particulates. No significant inhalation exposure to workers is expected as the notified chemical will be imported at a concentration of ≤ 10% within sealed cartridges. The notified chemical has low water solubility and if inhaled at low levels is likely to be readily cleared from the upper respiratory tract through mucocillary action.

Printing and Sandblasting of end products

Dermal exposure of workers to the notified chemical (at ≤ 10% concentration) may occur in the event of accidental rupture of the cartridges containing the notified chemical or during printing and sandblasting operations. Provided adequate control measures and safe work practices are in place to minimise worker exposure, including PPE, the risk to workers from the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

The notified chemical is for industrial and commercial use and will not be available to the public. The public may come into contact with 3D printed parts containing the notified chemical. However, the notified chemical is expected to be bound within a polymer matrix and not available for exposure.

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

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia in purpose-designed sealed printer cartridges. Accidental spillage of the ink containing the notified chemical will only occur if the cartridge is breached and spills are expected to be collected for disposal to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The printing processes are fully enclosed and automated. During maintenance, a small amount of residual notified chemical may need to be removed from the printer. This will be done using an industrial vacuum cleaned fitted with a HEPA filter. The filter will be bagged and disposed of to landfill in accordance with local government regulations.

Once the notified chemical has been fused into the polymer matrix to form the 3D printed object, it will generally not be available for release. Subsequent process will involve sand blasting, which will take place within an enclosed chamber. Small particles of fused polymer and notified chemical may be dislodged from the printed part during sand blasting. This will end up in a waste bag attached to the chamber. The wastes will be collected and disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM DISPOSAL

As estimated by the notifier, up to 1% of the import volume of the notified chemical may remain as residual in the spent cartridges. This will be disposed of to landfill in accordance with local government regulations along with the cartridges.

7.1.2. Environmental Fate

Based on its use as a material for 3D printing, most of the notified chemical is expected to share the fate of the printed 3D objects, which will be disposed of to landfill at the end of their useful lives. In landfill, the notified chemical will be present as cured solids and will be neither bioavailable nor mobile. Therefore, release of the notified chemical to the aquatic environment will be limited from the reported use pattern.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated as release of the notified chemical to the aquatic environment will be limited based on its reported use pattern.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 > 101 mgWAF*/L	Not harmful to fish up to its water solubility limit.
Daphnia Toxicity	48 h EC50 > 21 mg/L	Not harmful to aquatic invertebrates up to its water solubility limit.
Algal Toxicity	72 h EC50 > 11 mg/L	Not harmful to alga up to its water solubility limit.
Earthworm Toxicity	14 d EC 50 > 1000 mg/kg soil	Not harmful to earthworms.

*WAF: Water accommodated fraction

Based on the above ecotoxicological endpoints for the notified chemical, it 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) for acute and chronic toxicities (United Nations, 2009). The notified chemical is similarly not harmful to earthworms (Mensink et al., 1995).

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated as the notified chemical is not considered to be harmful to aquatic organisms up to its water solubility limit.

7.3. Environmental Risk Assessment

A Risk Quotient (PEC/PNEC) has not been calculated as the notified chemical is not harmful to its water solubility limit and release to the aquatic environment will be limited, based on its reported use pattern. Therefore, based on the low hazard and use as a material for 3D printing, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point > 450 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Differential Scanning Calorimeter (DSC). No phase transitions or significant thermal events observed. No change in appearance of test substance. Particle size data available.
Test Facility	Envigo (2017a)

Density 6,740 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Gas comparison pycnometer. Particle size data available.
Test Facility	Envigo (2017a)

Vapour Pressure 6.3×10^{-7} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Balance method. Test substance did not change in appearance under the conditions of the test. Particle size data available.
Test Facility	Envigo (2017c)

Water Solubility $\leq 6.14 \times 10^{-3}$ 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	Envigo (2017a)

Surface Tension 72.2 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Concentration: 0.053 mg/mL and 0.0515 mg/mL. Ring method. Particle size data available.
Test Facility	Envigo (2017a)

Particle Size

Method Compatible with EC Guidance Document EUR 20268 'Determination of Particle Size Distribution, Fibre Length and Diameter Distribution of Chemical Substances' (2002)

Range (µm)	*Mass (%)*
0 – 100 µm	78.4%
0 – 10 µm	≤ 0.87%
0 –5 µm	< 0.1%

Remarks	Particles were initially screened using a sieve followed by additional analysis using a cascade impactor.
Test Facility	Envigo (2017a)

Flammability Not highly flammable.

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids)
Remarks	Test substance melted but did not ignite when exposed to flame. Batch number of test substance: 050214. No particle size data provided.
Test Facility	Safepharm (2005a)

Flammability < 1L/kg/hour

Method	EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water)
Remarks	No signs of gas evolution or spontaneous ignition. Maximum gas evolved in a one hour period was between 2 – 4 mL. Particle size data available.
Test Facility	Envigo (2017b)

Pyrophoric Properties Non-pyrophoric

Method	EC Council Regulation No 440/2008 A.13 Pyrophoric Properties of Solids and Liquids
Remarks	No signs of ignition during dropping of sample onto non-combustible board, or within 5 minutes of powder settling on board. Particle size data available.
Test Facility	Envigo (2017b)

Autoignition Temperature > 400 °C

Method	EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids
Remarks	Temperature programmed laboratory oven. Colour of test substance changed from dark blue to yellow over course of test. Particle size data available.
Test Facility	Envigo (2017b)

Explosive Properties

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	Predicted to be negative based on the chemical structure not having any structural alerts that would imply explosive properties. Particle size data available.
Test Facility	Envigo (2017b)

Oxidizing Properties

Method	EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids)
Remarks	Test substance and cellulose mixture burnt but self extinguished without propagating combustion.
Test Facility	Envigo (2017b)

Immersion Corrosion Test of Metal Non-corrosive to metal

Method	Compatible with the United Nations Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria, Sixth Revised Edition [United Nations (2015)], Section 37.4 Test C.1: Test for determining the corrosive properties of liquids and solids that may become liquid during transport as dangerous good of Class 8, packing group III.
Remarks	Aluminium and steel pieces were exposed to the test substance in a cup-like reaction receptacle with reflux condenser at 55 °C for 7 days above the test substance (gas phase), half in the test substance and dipped into the solid. The test was considered positive if the mass loss of the metal specimens was greater than that described in the method. There was no appearance of rust on either the aluminium or steel pieces exposed to the test substance. The maximum corrosion rate for both pieces following exposure was 0.01 mm/year. Particle size data available.
Test Facility	NKKK (2016)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method EC Commission Directive 2004/73/EC Method B.1 *tris* Acute Toxicity (Oral)
Species/Strain	Rat/Sprague-Dawley CD (Crl: CD® (SD) IGS BR)
Vehicle	Arachis oil BP
Remarks - Method	GLP compliant. No deviations from protocol. The test substance was provided in powder form (no particle size data provided)with animals exposed to the test substance as a suspension.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 F	300	0/3
2	3 F	2,000	0/3
3	3 F	2,000	0/3

LD50	> 2,500 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity.
Effects in Organs	No abnormalities were recorded.
Remarks - Results	All animals made the expected body weight gains. One female in group 3 exhibited less weight gain during week 2 than the other females in the group. However, the overall weight gain was within the expected amount.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Safepharm (2005b)

B.2. Irritation – skin (*in vitro* EpiSkin™ Reconstructed Human Epidermis Model)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method EpiSkin™ Reconstructed Human Epidermis Model.
Vehicle	None
Remarks - Method	GLP compliant. No significant deviations from the protocol. Negative control: Dulbecco's Phosphate Buffered Saline (DPBS) with Ca^{++} and Mg^{++}. Positive control: Sodium Dodecyl Sulphate (5% w/v)

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.844	100	14.2
Test substance	0.958	113.5	13.6
Positive control	0.094	11.1	1.5

OD = optical density; SD = standard deviation

Remarks - Results	The test substance directly reduced MTT and showed potential to cause colour interference. However, as no interference due to direct reduction of

	MTT was observed when tested on water-killed tissues, and no colour interference was observed in colour correction tissues (performed in parallel) the study authors did not perform a quantitative correction of results. Positive and negative controls performed as expected.
CONCLUSION	The notified chemical was not irritating to the skin under the conditions of the test.
TEST FACILITY	Envigo (2017d)

B.3. Irritation – eye (*in vitro* Bovine Corneal Opacity and Permeability Assay)

TEST SUBSTANCE	Notified chemical (at 20% concentration)
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage Method B.47 of Commission regulation (EC) No. 440/2008
Vehicle	Sodium chloride 0.9% w/v
Remarks - Method	GLP compliant. No significant deviations from the protocol. Negative control: Sodium chloride 0.9% w/v. Positive control: Imidazole 20% w/v.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	0.67 (± 0.58)	0.03 (± 0.01)	1.07 (± 0.71)
*Test substance**	13.90 (± 3.22)	0.04 (± 0.05)	14.54 (± 2.5)
*Positive control**	66.96 (± 9.29)	1.74 (± 0.25)	93.04 (± 6.04)

SD = Standard deviation; IVIS = *in vitro* irritancy score
*Corrected for background values

Remarks - Results	Corneas exposed to the test substance were a pale blue colour at the end of the study. Positive and negative controls performed as expected.
CONCLUSION	No prediction of eye irritation can be made for the notified chemical under the conditions of the test.
TEST FACILITY	Envigo (2017e)

B.4. Irritation – eye [*in vitro* EpiOcular™ EIT (OCL-200)]

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 492 Reconstructed Human Cornea-like Epithelium (RhCE) Model - EpiOcular™ EIT (OCL-200)
Vehicle	None.
Remarks - Method	GLP compliant. No significant deviations from the protocol. Negative control: Distilled water. Positive control: Methyl acetate.

RESULTS

Test material	*Mean OD_{570} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.594	100
Test substance	1.019	63.9
Positive control	0.475	29.8

OD = optical density

Remarks - Results: Positive and negative controls performed as expected.

CONCLUSION: The notified chemical was considered to be not irritating to the eye under the conditions of the test.

TEST FACILITY: CERI (2017)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse/CBA/CaOlaHsd
Vehicle: Propylene glycol
Preliminary study: Yes
Positive control: Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using phenylacetaldehyde (> 90%).
Remarks - Method: GLP compliant.
No significant deviations from the protocol.

The notified chemical showed no clinical signs of toxicity or excessive irritation at a concentration of 50% w/w in a preliminary screening test.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4 F	868.31	-
10	4 F	929.18	1.07
25	4 F	833.18	0.96
50	4 F	1373.31	1.58

Remarks - Results: Blue coloured staining was observed on the ears and fur of animals exposed to the test substance.
No signs of systemic toxicity were observed. All animals made the expected weight gains.
The negative control performed as expected

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY: Envigo (2017f)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA$^-$
Metabolic Activation System	S9 mix from phenobarbitone/β-naphthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 50, 150, 500, 1,500, 5,000 µg/plate b) Without metabolic activation: 50, 150, 500, 1,500, 5,000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	GLP compliant. No significant deviation from the protocol. Test substance (particle size data not provided) was insoluble and was applied as a suspension to bacterial strains. A preliminary toxicity test indicated that the tests substance was non-toxic to strains TA100 and WP2uvrA$^-$ in the presence or absence of metabolic activation up to 5,000 µg/plate. Positive controls: without metabolic activation – N-ethyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535, WP2uvrA$^-$), 9-Aminoacridine (TA1537), 4-Nitroquinoline-1-oxide (TA98); with metabolic activation – 2-Aminoanthracene (TA100, TA1535, TA1537, WP2uvrA$^-$), benzo(a)pyrene (TA98).

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	*	negative
Test 2	> 5,000	≥ 5,000	*	negative
Present				
Test 1	> 5,000	≥ 5,000	*	negative
Test 2	> 5,000	≥ 5,000	*	negative

* The test substance was applied as a suspension.

Remarks - Results	A range finding test (test 1) determined a concentration range of 50 to 5,000 µg/plate for all bacterial strains tested and in the presence or absence of metabolic activation. No visible reduction in the bacterial background lawn was observed at any concentration level in the absence or presence of metabolic activation in either test 1 or test 2. The study authors noted that a grey colour was observed at 5,000 µg/plate with an associated black precipitate visible under a light microscope. The discolouration and precipitate did not affect the scoring of revertant colonies. No significant increases in the frequency of revertant colonies were recorded for any of the strains of bacteria, at any concentration level either with or without metabolic activation in either test 1 or test 2.

	All of the positive control chemicals used in the test induced significant increases in the frequency of revertant colonies with or without metabolic activation, confirming the sensitivity and activity of the S9-mix.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm (2004)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Ecotoxicological Investigations

C.1.1 Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Static
Species	*Gobiocypris rarus*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	145 mg $CaCO_3$/L
Analytical Monitoring	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
Remarks – Method	No significant deviations from the test guidelines were reported. A limit test was conducted using a nominal test concentration of 101 mg/L, prepared by adding 505 mg of test substance in 5 L of test water, stirring for 144 h and standing for 24 h. Then, 4.5 L of supernatant of the suspension was siphoned as the Water Accommodated Fraction (WAF). Caesium (Cs) and tungsten (W) concentrations in the test medium were measured at 0 h and 96 h.

RESULTS

Concentration		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
Control	<LOQ*	7	0
101 mg WAF/L	12.7 mgCs/L + 52.4 mgW/L	7	0

*LOQ: limit of quantification of 0.109 µg/L for Cs and 0.449 µg/L for W

LC50	>101 mgWAF/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The dissolved oxygen concentration in the test solution during the test was ≥ 69%. The measured Cs and W concentrations during 96 h exposure were within 80% to 120% of the initial value.
CONCLUSION	The test substance is not harmful to fish up to its water solubility limit.
TEST FACILITY	Guangdong Detection Center of Microbiology (2017a).

C.1.2 Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia - Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	ICP-MS
Remarks - Method	No significant deviations from the test guidelines were reported. The study was conducted as a limit test. An excess (50 mg/L) of test item was stirred in test water at approximately 1500 rpm for 24 hours. After the stirring, any undissolved test item was removed by filtration to produce a 100% v/v saturated solution of the test item. Cs and W concentrations in the test medium were measured at 0 h and 48 h.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
50	21	20	0	0

LC50	> 21 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. There was no significant change in the measured test concentration at 48 h so the results are based on 0 h measured test concentration. During the test, dissolved oxygen was ≥ 8.1 mg/L at 21°C (≥ 91% saturation; USGS 2011).
CONCLUSION	The test substance is not harmful to aquatic invertebrates up to its water solubility limit.
TEST FACILITY	Envigo (2017g)

C.1.3 Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 761/2009 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0%, 3.2%, 10%, 32% and 100% saturated solution Actual: 0.13, 0.34, 0.97, 3.6, 11 mg/L
Auxiliary Solvent	None
Water Hardness	Not provided
Analytical Monitoring	ICP-MS
Remarks - Method	No significant deviations from the test guidelines were reported. An excess (50 mg/L) of test item was stirred in test water at approximately 1500 rpm for 24 hours. After the stirring, any undissolved test item was removed by filtration to produce a 100% v/v saturated solution of the test item. This saturated solution was further diluted to obtain the test concentrations. Cs and W concentrations in the test medium were measured at 0 h and 72 h.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 11	0.97	> 11	0.97

Remarks - Results	All validity criteria for the test were satisfied. The mean cell density of the control increased 146 times after 72 h. There was no significant change in the measured test concentration at 72 h so the results are based on 0 h measured test concentration.
CONCLUSION	The test substance is not harmful to alga up to its water solubility limit.
TEST FACILITY	Envigo (2017h)

C.1.4 Acute toxicity in earthworm

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 207 Earthworms, Acute Toxicity Tests
Species	*Eisenia foetida*
Auxiliary solvent	None
Exposure Period	14 days
Remarks – Method	No significant deviations from the test guidelines were reported. The study was conducted as a limit test.

RESULTS

Concentration mg/kg		*Number of Earthworms*	*Mortality (%)*
Nominal(mg/kg)	*Actual*		*14 days*
Control	Control	40	7.5
1000	Not determined	40	7.5

LC50	>1000 mg/kg at 14 days
Remarks – Results	All validity criteria for the test are satisfied.

CONCLUSION	The test substance is not harmful to earthworms.
TEST FACILITY	Guangdong Detection Center of Microbiology (2017b).

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