File No.: LTD/2141

August 2020

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

EXP1501013

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019* (the IC Act) and *Industrial Chemicals (General) Rules 2019* (the IC Rules) by following the *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019* (the Transitional Act) and *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019* (the Transitional Rules). The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is administered by the Department of Health, and conducts the risk assessment for human health. 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 AICIS website. For enquiries please contact AICIS at:

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Executive Director
AICIS

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SUMMARY

The following details will be published on the AICIS website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2141	IMCD Australia Pty Ltd	EXP1501013	ND*	≤ 3 tonnes per annum	Component of automotive lubricants

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
As only limited toxicity data were provided, the assessed polymer 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
Under the conditions of the occupational settings described, the assessed polymer is not considered to pose an unreasonable risk to the health of workers.

When used in the proposed manner, the assessed polymer 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 assessed polymer 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 safe work practices to minimise occupational exposure during handling of the assessed polymer during reformulation:
  - Avoid contact with skin and eyes

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 assessed 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 assessed polymer should be handled by physical containment, collection and subsequent safe disposal.

Disposal

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

Regulatory Obligations

Specific Requirements to Provide Information
This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under section 101 of the IC Act the introducer of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed polymer is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if:

- the polymer has a number-average molecular weight of less than 1000 g/mol;
- the function or use of the polymer has changed from a component of automotive lubricants, 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 human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

Safety Data Sheet
The SDS of the assessed polymer provided by the applicant was reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND APPLICATION DETAILS

APPLICANT
IMCD Australia Pty Ltd (ABN: 44 000 005 578)
1st Floor, 372 Wellington Road
MULGRAVE VIC 3170

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

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
Data items and details taken to be protected information include: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, polymer constituents, residual monomers/impurities, additives/adjuvants, use details, import volume and identity of recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are varied for hydrolysis as a function of pH, partition coefficient, adsorption/desorption, dissociation constant, flash point, flammability, autoignition temperature, explosive properties and oxidising properties.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT
None

APPLICATION IN OTHER COUNTRIES
Japan (2017)
USA (2019)
China (2019)
New Zealand (2019)
Canada (2020)

2. IDENTITY OF CHEMICAL

MARKETING NAME
EXP1501013

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

ANALYTICAL DATA
Reference NMR, IR, GPC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 99%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: viscous, amber liquid

Property	*Value*	*Data Source/Justification*
Freezing Point	-25 to -34 °C	Measured
Boiling Point	Decomposes without boiling at ~265 °C	Measured
Density	863 kg/m^3 at 23.1 °C	Measured
Kinematic Viscosity	4.93 × 10^{-3} m^2/s at 40 °C	Measured
Vapour Pressure	4.11 × 10^{-8} kPa at 20 °C	Measured

Property	*Value*	*Data Source/Justification*
Water Solubility	1×10^{-4} g/L at 20 °C Water extractability < 2% (w/w)	Estimated (SDS) Measured
Hydrolysis as a Function of pH	Not determined	Could not be determined due to lack of analytical method, but contains functional groups that slowly hydrolyse under environmental conditions (pH 4-9)
Partition Coefficient (n-octanol/water)	Not determined	Could not be measured due to lack of analytical method but expected to partition to organic phase due to low solubility in water
Adsorption/Desorption	Not determined	Could not be measured but expected to sorb to soil based on low solubility in water
Dissociation Constant	Not determined	Could not be determined due to low water solubility but contains potentially cationic functionalities and is likely ionised in the environmental pH range of 4-9
Flash Point	> 220 °C	Estimated (SDS)
Flammability	Not determined	Based on flashpoint
Autoignition Temperature	Not determined	Not expected to autoignite
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 assessed polymer is expected to be stable under normal conditions of use.

Physical Hazard Classification
Based on the limited physico-chemical data depicted in the above table, the assessed polymer cannot be 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 ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS
The assessed polymer will not be manufactured in Australia. The assessed polymer will be imported into Australia as a component of lubricant additive packages at < 60% concentration, or in finished lubricants at < 10% concentration.

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

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

PORT OF ENTRY
Melbourne

TRANSPORTATION AND PACKAGING
The assessed polymer will be imported as a component of lubricant additive packages (at < 60% concentration) in iso-containers or 250 L steel drums. The lubricant additive packages will be transported by road to the distributor's warehouse facilities for storage, followed by distribution to industrial customers for reformulation. The finished lubricants (containing the assessed polymer at < 10% concentration) will then be transported to industrial end-users in drums, intermediate bulk containers and road tankers.

The assessed polymer will also be imported as a component of finished lubricants at < 10% concentration in drums or iso-containers, transported to distributor warehouses and then distributed to industrial end-users.

USE

The assessed polymer will be used at < 10% concentration in automotive lubricants, including transmission fluids and engine oils.

OPERATION DESCRIPTION

Reformulation

At the reformulation site, the lubricant additive package containing the assessed polymer (at < 60% concentration) will be transferred into a storage tank via a drum transfer system using hosing or be sourced directly from its drum. The assessed polymer will typically be pumped out from the storage tank/drum into a closed mixing vessel (through closed piping), to which other ingredients will be added. The finished products containing the assessed polymer (at < 10% concentration) will be dispensed into containers of varying size via an automated filling line. Quality control technicians may sample the finished products containing the assessed polymer (at < 10% concentration).

End-use

Finished products containing the assessed polymer (at < 10% concentration) will be applied by factory workers in automotive manufacturing facilities to vehicle engines and gearboxes using automated filling processes. These finished products will also be manually added to vehicle engines and gearboxes by mechanics at car service facilities.

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	Not specified	Not specified
Blending operators	0.16	3
Quality control technicians	0.16	3
Packaging workers	0.16	3
End use operators	0.16	3

EXPOSURE DETAILS

Transport and storage

Transport and storage workers are not expected to be exposed to the assessed polymer at < 60% concentration except in the unlikely event of an accident.

Reformulation

During reformulation, dermal and ocular exposure to the assessed polymer at < 60% concentration may occur during transfer to the mixing vessel, blending, quality control analysis, filling/packaging processes, and cleaning and maintenance of equipment. Given its low vapour pressure (4.11×10^{-8} kPa at 20 °C) and high viscosity (4.93×10^{-3} m^2/s at 40 °C), inhalation exposure to the assessed polymer is not expected. According to the applicant, worker exposure to the assessed polymer will be minimised through the use of enclosed and automated systems, local exhaust ventilation and personal protective equipment (PPE: protective clothing, goggles and impervious gloves) by workers.

End-use

Workers at automotive manufacturing or service facilities may also experience dermal and ocular exposure to end-use products containing the assessed polymer at < 10% concentration during addition of lubricants into vehicle engines and gearboxes, and during vehicle cleaning and maintenance. The potential for dermal and ocular exposure may be mitigated through the use of appropriate PPE.

6.1.2. Public Exposure
Finished lubricants containing the assessed polymer at < 10% concentration will be for industrial use only and will not be made available to the public.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the assessed polymer are summarised in the following table. For details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Acute oral toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity
Acute inhalation toxicity – rat	LC50 > 2.11 mg/L/4 hour; expected low toxicity
Repeat dose oral toxicity – rat, 28 days	NOAEL* = 1,000 mg/kg bw/day

*The authors of this study established a NOEL > 1,000 mg/kg bw/day

Toxicokinetics
No toxicokinetic studies were submitted for the assessed polymer.

Based on its high molecular weight (> 1,000 g/mol), absence of low molecular weight species < 1,000 g/mol and estimated low water solubility (1×10^{-4} g/L at 20 °C), absorption across biological membranes is expected to be limited.

Acute Toxicity
Based on studies conducted in rats, the assessed polymer is of low acute oral toxicity and is expected to be of low acute toxicity via inhalation.

Irritation and Sensitisation
No irritation or sensitisation studies were submitted for the assessed polymer.

The assessed polymer contains amine groups, which are functional groups of concern for corrosion/skin irritation (Hulzebos *et al.,* 2005). However, the potential for irritation is likely to be minimised by the high molecular weight of the assessed polymer (> 1,000 g/mol) and absence of low molecular weight species (< 1,000 g/mol).

Repeated Dose Toxicity
A 14-day repeated dose oral toxicity range finding study and a 28-day repeated dose oral toxicity study (with a 14-day recovery period) were submitted for the assessed polymer. In both studies, rats were administered with the assessed polymer at 100, 300 and 1,000 mg/kg bw/day. No mortalities or treatment-related adverse effects were observed in both studies. Although the study authors have established a NOEL > 1,000 mg/kg bw/day, treatment-related non-adverse effects were reported below this dose level. These included statistically significant effects in large unstained cell counts (≥ 300 mg/kg bw/day), blood calcium concentrations (≥ 100 mg/kg bw/day) and albumin to globulin ratio (≥ 1,000 mg/kg bw/day) in males, and statistically significant effects in blood creatinine, blood glucose and urine protein concentration in females at 1,000 mg/kg bw/day. Therefore, a No Observed Adverse Effect Level (NOAEL) of 1,000 mg/kg bw/day is established for the assessed polymer based on the results of this study.

Mutagenicity/Genotoxicity
No mutagenicity/genotoxicity studies were submitted for the assessed polymer.

Health Hazard Classification
As only limited toxicity data were provided, the assessed polymer 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
Based on the information available the assessed polymer is expected to be of low hazard. The assessed polymer may have potential for skin and eye irritation; however, the potential for irritation is likely to be minimised by the high molecular weight of the assessed polymer (> 1,000 g/mol) and absence of low molecular weight species (< 1,000 g/mol).

There may be potential for dermal and ocular exposure to the assessed polymer at < 60% concentration during reformulation; however, this should be minimised by the use of enclosed/automated processes, local exhaust ventilation and PPE, including protective clothing, impervious gloves and goggles, as stated by the applicant.

Workers at automotive manufacturing or service facilities may also experience dermal and ocular exposure to end-use products containing the assessed polymer at < 10% concentration during addition of lubricants into vehicle engines and gearboxes, and during vehicle cleaning and maintenance. Exposure may be mitigated where PPE is used. At this low use concentration, significant irritation effects of the assessed polymer are not expected.

Overall, under the conditions of the occupational settings described, the assessed polymer is not considered to pose an unreasonable risk to the health of workers.

6.3.2. Public Health

Finished lubricants containing the assessed polymer at < 10% concentration will be for industrial use only and will not be made available to the public, hence public exposure is not expected. Therefore, when used in the proposed manner, the assessed polymer 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 assessed polymer will be imported into Australia as finished lubricants, or as a component of lubricant additive packages for reformulation. Lubricant blending activities are expected to take place in enclosed blending facilities. Any accidental release during blending is expected to be collected for recycling or disposal by an approved waste management company.

RELEASE OF CHEMICAL FROM USE

Some losses of the assessed polymer are expected while adding the finished oil to the transmission or from the transmission itself from drips, but it is expected to be minimal. These losses are expected to be cleaned up using an adsorbent/absorbent material such as a rag, newspaper etc. and is expected to be disposed of to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

At the end of their useful lives, the products containing the assessed polymer will be drained from engines or transmissions for disposal. Used oil containing the assessed polymer is expected to be collected and re-refined or disposed of by approved waste management contractors, in accordance with local government regulations. Some of the residual fluid within the engines or transmissions will have the same fate as the machinery, which may be recycled as scrap metal or disposed of to landfill. A small proportion of the assessed polymer may also remain in end-use containers. Residues of the assessed polymer in empty containers are likely to either to share the fate of the container and be disposed of to landfill, or recycling through an approved waste management facility.

7.1.2. Environmental Fate

The assessed polymer is not biodegradable (Appendix C), but is not expected to be bioaccumulative due to its high molecular weight. Most of the assessed polymer will be either thermally decomposed during metal recycling of engines or transmissions, or re-refinement. Assessed polymer disposed of to landfill is expected to sorb to soil. The assessed polymer is expected to eventually degrade into water and oxides of carbon and nitrogen by abiotic and biotic processes in landfill, or by thermal decomposition in industrial facilities.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated for the assessed polymer, as no significant release to the aquatic compartment is expected from the proposed use pattern.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the assessed polymer are summarised in the table below. The results are based on nominal loading rates. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LLR50 > 100 mg/L (WAF)	Not harmful to fish up to its water solubility limit
Daphnia Toxicity	48 h ELR50 > 100 mg/L (WAF)	Not harmful to aquatic invertebrates up its water solubility limit
Algal Toxicity	72 h ErLR50 > 100 mg/L (WAF)	Not harmful to algae up to its water solubility limit

WAF: Water Accommodated Fraction

Based on the above ecotoxicological endpoints for the assessed polymer, it not expected to be harmful to aquatic life. Therefore, the assessed polymer 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

The predicted no-effect concentration (PNEC) has not been calculated as the submitted ecotoxicological studies indicate that the assessed polymer is not expected to be harmful to aquatic life.

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) for the aquatic compartment has not been calculated, as release to the aquatic compartment is not expected and the assessed polymer is not expected to be harmful to aquatic life. The assessed polymer is not readily biodegradable but does not bioaccumulate. Therefore, on the basis of the low hazard, low expected aquatic exposure and the assessed use pattern, the assessed polymer is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point -25 to -34 °C

Method	OECD TG 102 Melting Point/Melting Range
Remarks	Freezing range represents the temperature when the test substance started to harden and became frozen or stopped freezing.
Test Facility	Maxxam (2017a)

Boiling Point Decomposes without boiling at ~265 °C

Method	OECD TG 103 Boiling Point
Remarks	Determined using ebulliometric method. Boiling point/range could not be determined from duplicate measurements as the test substance underwent degradation prior to reaching a boiling point. The study authors note that the test substance appeared to be a slightly darker orange colour before heating, transitioning to dark brown with a tinge of orange at the decomposition temperature. At 300 °C, the study authors noted that the test substance was dark black, with vapour forming in the flask.
Test Facility	Maxxam (2017a)

Density 863 kg/m^3 at 23.1 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Determined using polypropylene tube method.
Test Facility	Maxxam (2017a)

Kinematic Viscosity 4.93×10^{-3} m^2/s at 40 °C

Method	ASTM D445 Kinematic Viscosity
Remarks	No detail on study method, results and discussion provided in the submitted report.
Test Facility	SWRI (2018)

Vapour Pressure 4.11×10^{-8} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure (2006)
Remarks	Determined using spinning rotor gauge method. The authors of this study note that though the measured vapour pressure was below the recommended range of this method, the coefficient of variance between replicates (n=3) was below the estimated repeatability criteria for this method.
Test Facility	EAG (2017)

Water Solubility < 2% (w/w)

Method	OECD TG 120 Water extractability instead of OECD TG 105 Water Solubility
Remarks	Since there was no suitable analytical method for quantification in a water solubility test, water extractability test was used as a modified version of flask method.
Test Facility	Maxxam (2017b)

Hydrolysis as a Function of pH

Method	OECD TG 111 Hydrolysis as a Function of pH
Remarks	Not determined due to lack of a suitable analytical method for quantification of assessed polymer.
Test Facility	Maxxam (2017c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat, Fixed Dose

TEST SUBSTANCE	Assessed polymer
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method (2001) EC Directive92/69/EEC B.1bis Acute Toxicity (Oral) Fixed Dose Method
Species/Strain	Rat/Wistar
Vehicle	Arachis oil BP
Remarks – Method	No deviations from the study protocol reported.

RESULTS

Sighting Study

Group	*Dose (mg/kg bw)*	*Evident Toxicity*	*Mortality*
1	300	No	0/1
2	2,000	No	0/1

Signs of Toxicity	No signs of toxicity reported.
Effects in Organs	No abnormalities observed at necropsy.
Remarks – Results	Animals showed expected body weight gain during the 14-day observation period.

Main Study

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	4F	2,000	0/4

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No signs of toxicity reported.
Effects in Organs	No abnormalities observed at necropsy.
Remarks – Results	All animals showed expected body weight gain during the 14-day observation period.

CONCLUSION	The assessed polymer is of low acute toxicity via the oral route.
TEST FACILITY	Envigo (2016a)

B.2. Acute Inhalation Toxicity – Rat

TEST SUBSTANCE	Assessed polymer
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009) EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation)
Species/Strain	Rat/Wistar (Han)
Vehicle	Low viscosity paraffinic oil (petroleum distillates, hydrotreated light paraffinic)
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	Mass median aerodynamic diameter (MMAD): 2.8–2.9 µm
Remarks – Method	No significant deviations from the study protocol reported. The reported relative humidity (6%) was much lower than recommended range in the OECD test guideline (30-70%). The study authors note that this value was considered appropriate for the relatively short exposure duration.

The study authors note that the assessed polymer at 100% concentration appeared very viscous and was unable to be aerosolised. Dilution of the assessed polymer at 75% (w/w) concentration with the vehicle, followed by heating the mixture to 100 °C generated the initial aerosol to a maximum concentration of 2 mg/L for the assessed polymer.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5M/5F	3.29	2.08* 2.11**	0/10

* Gravimetric time-weighted mean actual concentration of the assessed polymer
** Analytical time-weighted mean actual concentration of the assessed polymer

LC50	> 2.11 mg/L/4 hours
Signs of Toxicity	Slow breathing was noted for all animals during exposure. However, as no other signs of systemic toxicity were seen after exposure, the study authors did not consider the slow breathing to be of toxicological relevance.
Effects in Organs	One female animal presented with enlarged mandibular lymph nodes during necropsy. Study authors did not consider this finding toxicologically relevant on account of its nature and isolated incidence.
Remarks – Results	All animals showed expected body weight gain during the 15-day observation period.

CONCLUSION The assessed polymer is expected to be of low acute toxicity via inhalation.

TEST FACILITY CRL (2019)

B.3. Repeat Dose Oral Toxicity – Rat

TEST SUBSTANCE Assessed polymer

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral)

Species/Strain	Rat/Wistar (Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Arachis Oil BP
Remarks – Method	In a range finding study (Envigo CRS, 2016a), rats (3/dose/sex) were administered by gavage with the test substance at 100, 300 or 1,000 mg/kg bw/day for 14 days. No mortalities or substance-related toxicities were observed. No significant deviations from the study protocol were reported.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5M/5F	0	0/10
Low Dose	5M/5F	100	0/10
Mid Dose	5M/5F	300	0/10
High Dose	5M/5F	1,000	0/10

Control Recovery	5M/5F	0	0/10
High Dose Recovery	5M/5F	1,000	0/10

Mortality and Time to Death
No mortalities were recorded during the study period.

Clinical Observations
No treatment-related clinical signs were observed.

Increased incidences of irritability and vocalisation in high-dose females occurred during treatment weeks 3-4 and weeks 1-2 and 5, respectively. The frequency of these observations regressed to comparable levels with controls during recovery. Furthermore, the control group had incidences of vocalisation and irritability that were equivalent or greater than those seen in the low and mid-dose females. As the control group displayed vocalisation during treatment and recovery, the study authors did not consider the increase in vocalisation from the high dose group as toxicologically significant. The increased incidence of irritability was not seen as toxicologically significant by the study authors as high-dose females did not display irritability during the sensory reactivity test.

Laboratory Findings – Haematology, Clinical Chemistry, Urinalysis
No toxicologically relevant findings in haematology, clinical chemistry or urinalysis were noted.

Although statistically significant, the following changes were considered by the study authors to be of small magnitude, without a dose-response relationship and confined to one sex, and therefore attributable to normal biological variation or not toxicologically relevant:

- In male rats: decreases in large unstained cell counts (≥ 300 mg/kg bw/day), blood calcium concentrations (≥ 100 mg/kg bw/day), and albumin to globulin ratio (≥ 1000 mg/kg bw/day)
- In female rats: increases in blood creatinine and urine protein concentrations and a decrease in glucose (≥ 1000 mg/kg bw/day)

Notable increases and decreases in bile acid parameters in males and females, respectively, were not considered toxicologically relevant by the study authors as the increased bile acid concentration was attributed to atypical individual control values and all group mean values were within the historical control data.

Effects in Organs
No treatment-related organ weight changes or macroscopic or histopathological findings were observed.

High dose males displayed a statistically significant increase in mean adjusted adrenal weight during treatment; this had regressed to become comparable with controls following recovery.

Remarks – Results
No treatment-related effects were observed on body weight gain, food or water consumption.

Notably increased mean food consumption in high-dose females was observed during weeks 1-4 of treatment and during the first week of recovery. However, this observation was not seen by the end of the recovery period and was not accompanied by associated increases in mean body weight. Hence we determine that this observation is not related to treatment.

The study authors have established a NOEL >1,000 mg/kg bw/day. However, treatment-related non-adverse effects were reported below this dose level.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1,000 mg/kg bw/day, the highest dose tested.

TEST FACILITY Envigo CRS (2016b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Assessed polymer
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I) Test
Inoculum	Activated Sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	HPLC, Biochemical oxygen demand (BOD) and dissolved organic carbon (DOC)
Remarks – Method	Conducted in accordance with the test guideline above, and in compliance with GLP standards and principles. No major deviations from the test guideline were reported. A toxicity control was also conducted.

RESULTS

Test Substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	-1	7	76
28	-1	14	90
		28	94

Remarks – Results	All validity criteria of the test guideline were satisfied. The degradation of aniline surpassed the threshold level indicating the suitability of the inoculums. Oxygen uptake was 9.7 mg O_2/L in 28 days and did not exceed 10.2 mg/L. The pH was maintained between 7.3 – 7.6. The average percentage biodegradation of the test substance was 0% after 28 days.
CONCLUSION	The assessed polymer is not readily biodegradable.
TEST FACILITY	CERI (2016)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Assessed polymer
METHOD	OECD TG 203 Fish, Acute Toxicity Test -Static
Species	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	12 -29 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV/Total organic carbon (TOC)
Remarks – Method	The test was conducted according to good laboratory practice (GLP) principles. Following a range-finding test, a limit test for the definitive test was conducted with no major deviations from the test guidelines. Test solutions were prepared as water accommodated fractions (WAFs). Test concentrations were based on the nominal loading rates. Zinc sulphate heptahydrate was used as a reference substance.

RESULTS

Nominal Concentration (mg/L)	*Number of Fish*	*Mortality*			
		24 h	*48 h*	*72 h*	*96 h*
Negative Control	10	0	0	0	0
WAF Control	10	0	0	0	0
100	10	0	0	0	0

LLR50 > 100 mg/L (WAF) at 96 hours (nominal concentration)

Remarks – Results All validity criteria were fulfilled. Dissolved oxygen concentration at the end of the test was ≥ 60% of the air-saturation value in controls and test vessels. WAFs were stable within or ± 20% of the initial TOC. The 96 h lethal loading rate, LLR50 including the 95% confidence interval were calculated using the visual assessment as the statistical analysis of the data was not appropriate. The 96 h LC50 = 0.19 mg/L for fish exposed to zinc sulphate heptahydrate was within the range of expected responses.

CONCLUSION The assessed polymer is not harmful to fish up to its water solubility limit.

TEST FACILITY Maxxam (2017d)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Assessed polymer

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test – Static
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 80 - 110 mg $CaCO_3$/L
Analytical Monitoring TOC
Remarks – Method The test was conducted according to good laboratory practice (GLP) principles. No major deviations from the test guidelines were reported. Test solutions were prepared as water accommodated fractions (WAFs) and test concentrations were nominal loading rates. The test solutions were not renewed during the 48 h exposure. Zinc sulphate heptahydrate was used as a reference substance.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Number Immobilised*	
		24 h [acute]	*48 h [acute]*
Negative Control	20	0	0
WAF control	20	0	0
6.25	20	0	0
12.5	20	0	0
25	20	0	0
50	20	0	0
100	20	0	0

LC50 100 mg/L (WAF) at 48 hours (nominal concentration)

Remarks – Results All validity criteria were fulfilled. In the control, no daphnids were trapped at the surface of the water or showed signs of stress. Concentrations of dissolved oxygen were in the range 8.8 – 9.1 mg O_2/L equivalent to > 83% oxygen saturation in fresh water (USGS, 2011). The pH of test water was in the range of 8 to 8.1. Based on nominal loading rates, the 48 h effective loading rate, ELR50 was estimated to be > 100 mg/L for daphnids. The 48 h EC50 = 0.26 mg/L for daphnids exposed to zinc sulphate heptahydrate was within the range of expected responses.

CONCLUSION	The assessed polymer is not harmful to aquatic invertebrates up to its water solubility limit.
TEST FACILITY	Maxxam (2017d)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE	Assessed polymer
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	Freshwater Green Alga, *Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0 - 100 mg/L
Auxiliary Solvent	None
Water Hardness	None
Analytical Monitoring	TOC
Remarks – Method	The test was conducted according to good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. Test solutions were prepared as water accommodated fractions (WAFs). Five nominal loading rates (6.25, 12.5, 25, 50 and 100 mg/L) were used along with negative control and WAF control. Zinc sulphate heptahydrate was used as a reference substance.

RESULTS

Biomass		*Growth*	
EyLR50 (mg/L at 72 h)	*NOEyLR (mg/L)*	*EyLR50 (mg/L at 72 h)*	*NOEyLR (mg/L)*
> 100	100	> 100	100

Remarks – Results	All the validity criteria for the study were satisfied. The cell density in the control increased by a factor of 96 within 72 hours. The mean coefficient of variation for section-by-section specific growth rates in the control cultures was 27.76%. The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 3.64%. Due to the complex nature of the WAFs and the assessed polymer, the results are based on the test nominal loading rates. The 72 h ErLR50 was determined to be > 100 mg/L. The 72 h EC50 = 0.079 mg/L for algae exposed to zinc sulphate heptahydrate was within the range of expected responses.
CONCLUSION	The assessed polymer is not harmful to algae up to its water solubility limit.
TEST FACILITY	Maxxam (2017f)

BIBLIOGRAPHY

Aither (2013) Third Independent Review of the Product Stewardship (Oil) Act 2000. Canberra, Australia.

CERI (2016) Biodegradation study of EXP1501013 (Study No. 16231, April , 2016). Chemicals Evaluation and Research Institute, Kurume, Japan.

CRL (2019) Assessment of Acute Inhalation Toxicity with EXP1501013 in the Rat (Nose Only Exposure) (Study No. 20176428, May, 2019). 's-Hertogenbosch, The Netherlands, Charles River Laboratories Den Bosch BV (Unpublished report submitted by the applicant).

EAG (2017) Determination of the Vapor Pressure of EXP1501013 (Study No. 523K-101, September, 2017). Maryland, USA, EAG, Inc. (Unpublished report submitted by the applicant).

Envigo (2016a) EXP1501013: Acute Oral Toxicity in the Rat – Fixed Dose Method (Study No. 41501999, January, 2016). Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the applicant).

Envigo CRS (2016a) EXP1501013: Range Finding Study by Oral Gavage Administration to Han Wistar Rats (Study No. ZAC0041, March, 2016). Suffolk, UK, Envigo CRS Limited (Unpublished report submitted by the applicant).

Envigo CRS (2016b) EXP1501013: Toxicity Study by Oral Gavage Administration to Han Wistar Rat for 4 Weeks Followed by a 2 Week Recovery Period (Study No. ZAC0042, May, 2016). Suffolk, UK, Envigo CRS Limited (Unpublished report submitted by the applicant).

Hulzebos *et al.,* (2005) Use of structural alerts to develop rules for identifying chemical substances with skin irritation or skin corrosion potential. QSAR Combinatorial Science. 24:332-342.

Maxxam (2017a) Product Chemistry Testing of EXP1501013 (Study No. INFI900-170087, December, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

Maxxam (2017b), Determination of the Solution/Extraction Behaviour of EXP1501013 in Water (Study No. INFI900-170007, September, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

Maxxam (2017c) Expert Statement/Request for Test Exemption: Hydrolysis as a Function of pH of EXP1501013. (Study No. INFI900-170085, October, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

Maxxam (2017d) Acute Toxicity Test of EXP1501013 Using Rainbow Trout, Oncorhynchus Mykiss. (Study No. TOX1705, August, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

Maxxam (2017e) Acute Immobilisation Test of EXP1501013 Using Daphnia Magna. (Study No. TOX1704, August, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

Maxxam (2017f) 72-h Growth Inhibition Test of EXP1501013 Using Pseudokirchneriella Subcapitata. (Study No. TOX1703, August, 2017). British Columbia, Canada, Maxxam Analytics (Unpublished report submitted by the applicant).

SWRI (2018) [No study title] (October, 2018). Texas, U.S.A., Southwest Research Institute (Unpublished report submitted by the applicant).

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS), 3rd revised edition. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >

USGS (2011) U.S. Geological Survey, Change to solubility equations for oxygen in water: Office of Water Quality Technical Memorandum 2011.03, accessed https://water.usgs.gov/software/DOTABLES/ v 3.5., 8 January 2018.