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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Z-181

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1633	Lubrizol International Inc	Z-181	ND*	≤ 70 tonnes per annum	Component of metalworking fluids

* ND = Not Determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, 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.

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

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

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation and end-use:
  - Enclosed, automated processes, where possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation and end-use:
  - Avoid contact with skin and eyes

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

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

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

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
  - additional information becomes available on the (eco)toxicity of the notified chemical;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of metalworking fluids, 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.

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

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Lubrizol International Inc
28 River Street
SILVERWATER NSW 2128

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne 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, analytical data, degree of purity, impurities, additives/adjuvants, use details, import volume and analogue identity.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for melting point/boiling point, density, vapour pressure, adsorption/desorption, flash point, flammability, auto ignition temperature and all (eco)toxicological endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Canada, China, EU, New Zealand, Korea, Taiwan and USA

2. IDENTITY OF CHEMICAL

MARKETING NAME
Z-181

MOLECULAR WEIGHT
> 500 g/mol

ANALYTICAL DATA
Reference NMR, IR, MS, GPC, UV-Vis and TGA spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
~ 60 – 75%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Brown, waxy solid

Property	Value	Data Source/Justification
Pour point*	39 °C ± 3 °C (312 ± 3K)	Measured
Boiling Point*	~ 110 °C at 99 - 101.3 kPa	Measured
Density*	909 kg/m^3 at 20 ± 0.5 °C	Measured
Vapour Pressure*	5.55×10^{-4} kPa at 25 °C 2.68×10^{-3} kPa at 40 °C 3.47×10^{-3} kPa at 60 °C	Measured
Water Solubility	3.59 mg TOC**/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functional groups but significant hydrolysis is unlikely in the environmental pH

		range (4-9).
Partition Coefficient (n-octanol/water)	log P_{ow} > 10.0	Measured
Surface Tension*	66.5 ± 2.0 mN/m (for loading rate of 0.11 g/L), and 56.2 ± 1.0 mN/m (for loading rate of 1.1 g/L) at 22 ± 0.5 °C	Measured
Adsorption/Desorption*	log K_{oc} > 5.63	Measured
Dissociation Constant	Not determined	Does not contain dissociable functionality.
Particle Size	Not determined	Introduced in granular form
Flash Point*	109 ± 2 °C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be highly flammable based on the read-across flash point
Autoignition Temperature*	362 ± 5 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties.

* Properties of the analogue chemical (identity is exempt information)
** TOC- total organic carbon analysis

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported into Australia as an additive package for metal working fluids at 1 - 20% concentration for reformulation into end-use products at 0.1 – 20% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	30-40	35-45	45-50	55-60	60-70

PORT OF ENTRY
Western Australia, Queensland and Victoria

IDENTITY OF RECIPIENT
Lubrizol International Inc

TRANSPORTATION, STORAGE AND PACKAGING
The notified chemical will be imported into Australia as an additive package and transported via isotainer or 330 gallon (~1,250 L) containers. Smaller quantities will be transported in 55 gallon (~208 L) drums. The containers will be kept closed when not in use and precautions will be taken to avoid release into the environment.

USE
The notified chemical will be used as a component of metalworking fluids at 0.1 – 20% concentration.

OPERATION DESCRIPTION
The notified chemical imported as an additive package will be reformulated into end-use products.

Reformulation
At the reformulation facility, it is expected that the additive package containing the notified chemical at 1 – 20% concentration will be transferred into the blending tank where it would be mixed with mineral oil and possibly other additives using automated, ventilated and enclosed processes. After blending, it is expected that the end-use products containing the notified chemical at 0.1 – 20% concentration will be packaged using automated processes.

End-use
Metalworking fluids containing the notified chemical at 0.1 – 20% concentration will be used by professional workers in industrial settings. The metalworking fluids are expected to be pumped from the containers.

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)*
Workers involved in blending operations	1 - 3	3 - 4
Workers involved in packaging operations	2 - 4	1 - 3
Distribution	0 - 2	50 - 60

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may come into contact with the notified chemical at ≤ 20% concentration only in the event of accidental rupture of containers.

Reformulation
Dermal and ocular exposure of workers to the notified chemical at ≤ 20% concentration may occur during reformulation and dilution when connecting and disconnecting hoses and during sample testing. The blending and packaging processes are expected to be automated and in an enclosed systems with ventilation in place. Dermal and ocular exposure will also be possible when cleaning up spills or leaks and during maintenance of the blending equipment.

Dermal and ocular exposure of workers to the notified chemical is expected to be further mitigated through the use of personal protective equipment (PPE) including coveralls, safety glasses and impervious gloves. Inhalation exposure is not expected given the enclosed systems and the estimated low vapour pressure of the notified chemical.

End-use
Dermal, ocular and inhalation (if mists and vapours are generated) exposure of workers to the notified chemical at ≤ 20% concentration may occur when using the metalworking machinery and/or lathe units. It is expected that the metalworking processes will be mostly enclosed or supplied with engineering controls such as shielding and local ventilation to reduce exposure from splashes, mists and vapours (if generated). Exposure is expected to be further mitigated through the use of PPE (including goggles, face shield, gloves, protective clothing).

6.1.2. Public Exposure
The products containing the notified chemical will be for industrial use only. Therefore, exposure of the general public to the notified chemical is not expected.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on an analogue chemical (identity is exempt information) are summarised in the following table. For full details of the studies, refer to Appendix B. As the

analogue chemical has a composition similar to the notified chemical, it was considered adequate for hazard assessment of the notified chemical for human health endpoints.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay(LLNA)	no evidence of sensitisation
Rat, repeat dose oral toxicity combined with reproduction/developmental toxicity screening test	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome damage	non genotoxic
Genotoxicity – *in vitro* mammalian cell gene mutation test	non genotoxic

Toxicokinetics
Based on the relatively high molecular weight (> 500 Da), low water solubility (3.59 mg TOC/L at 20 °C) and high partition coefficient (Log Pow > 10.0), adsorption of the notified chemical across biological membranes is expected to be limited.

Acute toxicity
No acute toxicity data were submitted for the notified chemical. The analogue chemical was found to be of low toxicity via the oral and dermal routes in studies conducted in rats.

Irritation
No irritation data were submitted for the notified chemical. The analogue chemical was found to be slightly irritating to the skin and eyes in studies conducted in rabbits.

Sensitisation
No sensitisation data were submitted for the notified chemical. The analogue chemical was not a skin sensitiser in mice when tested at up to 25% concentration in a local lymph node assay.

Repeated dose toxicity and reproductive/developmental toxicity
No repeated dose toxicity data were submitted for the notified chemical.

A combined repeated dose oral (gavage) toxicity and reproduction/developmental toxicity screening test was conducted in rats, in which the analogue chemical was administered at 100, 300, 500 and 1000 mg/kg bw/day for 28 days (male animals) and 49-63 days (female animals) respectively.

The reproductive/developmental and systemic NOAEL was established as 1000 mg/kg bw/day, the highest dose tested, based on the absence of any treatment-related adverse effects.

Mutagenicity/Genotoxicity
No mutagenicity/genotoxicity data were submitted for the notified chemical. The analogue chemical was negative in a bacterial reverse mutation assay, an *in vitro* chromosome aberration test and an *in vitro* mammalian cell gene mutation test.

Health hazard classification
Based on the available information, 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.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Limited toxicological data on the notified chemical are available. Based on the analogue data, the notified chemical is expected to be of low hazard, presenting only as a mild skin and eye irritant.

During reformulation and end-use, workers may be exposed to the notified chemical at ≤ 20% concentration and therefore there is a potential risk of skin and eye irritation effects. The use of engineering controls such as

enclosed and automated processes along with appropriate PPE (including goggles, face shield, gloves, protective clothing), as recommended by the notifier, should limit worker exposure.

Based on the low exposure under the conditions of the occupational settings, the risk to workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

The products containing the notified chemical will be used in industrial settings only and will not be made available to the public.

Based on the assessed use patterns, the risk to the public is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as an additive package for reformulation into end-use rust inhibitor additive products. The reformulation process will involve blending the additive package containing the notified chemical with oil and other ingredients in an automated and enclosed process, followed by automated filling of the finished products into end-use containers. According to the notifier, similar materials and products are blended in the same equipment; therefore, any residual material left in the blending tank or transfer lines is simply allowed to remain for the next blend. Accidental spills of the notified chemical during reformulation, transport or storage are expected to be adsorbed onto a suitable material and disposal of in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The products containing the notified chemical will be diluted in metalworking baths before final application as a rust inhibitor additive in metal working fluids in industrial settings. The final fluids, containing the notified chemical are expected to be recirculated during use and refilled when required. The metal working fluids will be replaced when it reaches the end of its useful life. According to the notifier, the spent fluids are disposed of in two ways. In small facilities, it is likely to be disposed of to an authorised disposal company. In larger facilities, some waste handling may be done on site, where the spent fluids will be subjected to oil/water separation through ultra-filtration, and less than 1% of the notified chemical will remain in the wastewater as estimated by the notifier. The majority of the notified chemical will remain with the oil phase, and be sent to an authorised disposal company for disposal of safely. Accidental spills of the notified chemical during uses are expected to be adsorbed onto a suitable material and disposal of in accordance with local government regulations.

RELEASE OF CHEMICAL FROM DISPOSAL

The empty containers containing small amount of residue of the notified chemical are expected to be reused or disposed of by an authorised disposal company in accordant with local government regulations. Wastewater containing residual (< 1%) notified chemical may be disposed of, to sewer.

7.1.2. Environmental Fate

The biodegradability study conducted on the analogue chemical of the notified chemical (53% degradation after 28 days) indicated that the notified chemical is not readily biodegradable. For details of the biodegradability study, please refer to Appendix C. Based on its limited water solubility and highly hydrophobicity, the majority of the notified chemical released to sewers is likely to adsorb to sludge, and be removed effectively within the sewage treatment plants (STPs), prior to discharge to receiving waters. The waste sludge from STPs is expected to be disposed of to landfill in accordance with local regulations. In landfill, based on its limited water solubility, highly hydrophobicity and high adsorption coefficient, the notified chemical is expected to be immobile. The notified chemical in sludge and landfill is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

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

The results from ecotoxicological investigations conducted on the analogue chemical are summarised in the table below. Details of these studies can be found in Appendix C. As the analogue chemical has a composition similar to the notified chemical, it was considered adequate for hazard assessment of the notified chemical for environmental endpoints.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	EC50 > 100 mg/L (WAF*)	Not harmful to fish up to its water solubility limit
Daphnia Toxicity	EC50 > 100 mg/L (WAF*)	Not harmful to aquatic invertebrates up to its water solubility limit
Algal Toxicity	EC50 > 100 mg/L (WAF*)	Not harmful to alga up to its water solubility limit
Inhibition of Bacterial Respiration	EC50 > 1,000 mg/L	Does not inhibit microbial activity in STPs

*WAF: Water Accommodated Fraction

The results from ecotoxicological investigations on the analogue chemical indicate that the notified chemical is not harmful to aquatic life up to its water solubility limit. 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).

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, and no significant release of the notified chemical to the aquatic environment is expected from the proposed use pattern.

7.3. Environmental Risk Assessment

The Risk Quotient (PEC/PNEC) for the aquatic compartment has not been calculated as the notified chemical is not considered to be harmful to aquatic organisms and no significant release of the notified chemical to the aquatic environment is expected from the proposed use pattern. On the basis of the low hazard and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Pour Point 39 °C ± 3 °C

Method	OECD TG 102 Melting Point/Melting Range
Remarks	Stationary point was determined when the test substance was no longer mobile. Pour point was stationary point plus 3 °C.
Test Facility	Envigo (2016)

Boiling Point Approximately 110 °C at 99 - 101.3 kPa

Method	OECD TG 103 Boiling Point
Remarks	Determined using a differential scanning calorimeter
Test Facility	Envigo (2016)

Density 909 kg/m^3 at 20 ± 0.5 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Determined by a gas comparison pycnometer
Test Facility	Envigo (2016)

Vapour Pressure 5.55×10^{-4} kPa at 25 °C
2.68×10^{-3} kPa at 40 °C
3.47×10^{-3} kPa at 60 °C

Method	OECD TG 104 Vapour Pressure
Remarks	Determined using a vapour pressure balance
Test Facility	Envigo (2015a)

Water Solubility 3.59 mg TOC/L at 20 ± 0.5 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	Envigo (2017)

Partition Coefficient (n-octanol/water) log Pow > 10.0

Method	OECD TG 117 Partition Coefficient (n-octanol/water) EC Council Regulation No 440/2008 A.8 Partition Coefficient
Remarks	HPLC Method
Test Facility	Envigo (2017)

Surface Tension 66.5 ± 2.0 mN/m (for loading rate of 0.11 g/L), and 56.2 ± 1.0 mN/m (for loading rate of 1.1 g/L) at 22 ± 0.5 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	The test item was considered to be surface active but this was proportional to the loading rate.
Test Facility	Envigo (2016)

Adsorption/Desorption log K_{oc} > 5.63

Method	OECD TG 121 Adsorption - Desorption EC Council Regulation No 440/2008 C.19. Adsorption Coefficient
Remarks	HPLC method
Test Facility	Envigo (2015b)

Flash Point 109 ± 2 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Closed cup method
Test Facility	Envigo (2015c)

Autoignition Temperature 362 ± 5°C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Test Facility	Envigo (2015c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method EC Council Regulation No 440/2008 B.1 bis Acute toxicity (oral) fixed dose method
Species/Strain	Rat/ Wistar (RccHan: WIST)
Vehicle	Arachis oil BP
Remarks - Method	GLP certificate No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	2000	0/1
2	4 F	2000	0/4

LD50	> 2000 mg/kg bw
Signs of Toxicity	No clinical signs of toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	All animals showed expected body weight gains.

CONCLUSION	The test substance is of low acute toxicity via the oral route.
TEST FACILITY	Envigo (2015d)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 402 Acute Dermal Toxicity EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/Wistar (RccHan: WIST)
Vehicle	None
Type of dressing	Semi-occlusive
Remarks - Method	GLP Certificate No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M, 5F	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No signs of dermal irritation were noted.
Signs of Toxicity - Systemic	There were no deaths or clinical signs of systemic toxicity.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	The majority of the animals showed expected body weight gains. Two female animals showed no gains during week 1 but expected gains during week 2. Another female animal showed expected gain during week 1 but no gain during week 2.

CONCLUSION	The test substance is of low acute toxicity via the dermal route.
TEST FACILITY	Envigo (2015e)

B.3. Irritation – skin

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White (Hsdlf:NZW)
Number of Animals	2
Vehicle	Distilled water
Observation Period	7 days
Type of Dressing	Semi-occlusive
Remarks - Method	GLP certificate No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Erythema/Eschar	1	1	1	< 7 days	0
Oedema	0	1	1	< 7 days	0

* Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal

Remarks - Results	Very slight erythema and slight oedema were noted at both treated skin sites immediately after patch removal. Very slight erythema, with or without very slight oedema was noted at both treated skin sites at up to one hour after the patch removal and persisted up to the 72-hour observation. All the effects were resolved by day 7.
CONCLUSION	The test substance is slightly irritating to the skin.
TEST FACILITY	Envigo (2015f)

B.4. Irritation – eye

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation)
Species/Strain	Rabbit/New Zealand White (Hsdlf:NZW)
Number of Animals	2
Observation Period	72 hours
Remarks - Method	GLP certificate No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Conjunctiva: redness	0.7	0.7	2	< 72 hours	0
Conjunctiva: chemosis	0.3	0.3	2	< 48 hours	0
Conjunctiva: discharge	0.3	0.3	2	< 48 hours	0
Corneal opacity	0	0	0	-	0
Iridial inflammation	0	0	5	< 24 hours	0

* Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal

Remarks - Results	No corneal effects were observed during the study.

Iridial inflammation was observed in one treated eye 1 hour after the treatment.

Moderate conjunctival irritation was noted in both treated eyes 1 hour after treatment with minimal conjunctival irritation noted at 24 and 48- hour observations.

Both treated eyes were normal at the 72- hour observation.

CONCLUSION The test substance is slightly irritating to the eye.

TEST FACILITY Envigo (2015g)

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

TEST SUBSTANCE Analogue chemical (identity is exempt information)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/Ca
Vehicle Acetone/olive oil (4:1)
Preliminary study Yes
Positive control α-Hexylcinnamaldehyde
Remarks - Method GLP Certificate
No significant protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	3188.09 ± 700.76	-
0.25	5 F	4332.36 ± 1631.79	1.36
2.5	5 F	5172.42 ± 3033.56	1.62
25	5 F	5886.25 ± 2683.94	1.85
Positive Control			
25	5 F	31757.50 + 15605.02	9.96

EC3 Could not be calculated as the test substance at the highest concentration tested induced an SI of 1.85 (< 3).

Remarks - Results There were no unscheduled deaths, signs of systemic toxicity, local skin irritation or marked increases in ear thickness noted in the test or control animals. All animals showed expected gains in body weights.

Positive and negative controls produced satisfactory responses, thus confirming the validity of the test system.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance under the conditions of the test.

TEST FACILITY Envigo (2015h)

B.6. Repeat dose toxicity

TEST SUBSTANCE Analogue chemical (identity is exempt information)

METHOD OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

Species/Strain Rat/Sprague Dawley Crl:CD(SD)

Route of Administration	Oral – gavage
Exposure Information	Total exposure days: Male animals from 14 days pre-mating to 1 day prior to scheduled euthanasia for a total of 28 doses Female animals from 14 days pre-mating to lactation day 13 for a total of 49-63 doses Dose regimen: 7 days per week
Vehicle	Arachis oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	15M, 15F*	0	0/30
low dose	10M, 10F	100	0/20
mid dose	10M, 10F	300	0/20
high dose	10M, 10F	500	020
control recovery	15M, 15F*	1000	0/30

* 5 animals/sex were necropsied following a 15-day recovery period.

Mortality and Time to Death

All treated parental animals survived to the scheduled necropsies. The number of F1 pups (litters) found dead during the post-natal days (PND) 1-13, were 2, 5, 2, 3, 1 in the control (0), 100, 300, 500 and 1000 mg/kg bw/day groups, respectively.

Dose mg/kg bw/day	Mean number of pups born	Number of pups dead (lactation days)
0	15.1	2 (0, 3)
100	13.9	5 (0, 1, 7, 0, 0)
300	14.9	2 (0, 0)
500	15.2	3 (0, 0, 4)
1000	14.4	1 (3)

Clinical Observations

All treated animals showed increased incidence of red material around the nose. Male and female animals in the 300, 500 and 1000 mg/kg bw/day groups were reported to have red and/or clear material around the mouth approximately one hour post administration throughout the treatment period.

Other infrequent and non-dose-related clinical finding noted in all treatment groups included hair loss on various body surfaces. Other clinical findings were not reported.

Animals in all treatment groups showed no significant mean body weights and body weight gain changes throughout the study, except for female animals treated at 1000 mg/kg bw/day showing a statistically significantly higher mean body weight gain during the pre-mating period. In the absence of a corresponding effect on mean body weights, the difference in mean body weight gain in the 1000 mg/kg bw/day group was not considered by the study authors to be test substance-related. No changes in the food consumptions were noted in any treatment groups.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No significant effects were seen in all animals at 100, 300 and 500 mg/kg bw/day. In the highest dose recovery group male animals had lower mean serum total protein and female animals showed lower mean serum glucose. Higher mean haemoglobin distribution width was observed at primary necropsy in female animals in the 1000 mg/kg bw/day dose group. These effects were considered by the study authors to be attributed to biological variability.

Effects in Organs

Male animals in the 100 mg/kg bw/day dose group showed lower mean heart weight relative to final body weight (not statistically significant) at primary necropsy. Female animals in the 1000 mg/kg bw/day group showed higher mean absolute brain weight compared to control groups at the recovery necropsy. These effects

were considered by the study authors to be attributed to biological variability.

Microscopic examination showed no treatment-related effects at the primary necropsy.

Reproductive and developmental findings

Effects on Parental (P) animals
No effects on fertility and reproductive performance were observed. No treatment-related effects were observed on the oestrous cycles and the gestation lengths.

Effects on pups (F1)
The mean number of F1 pups born, live litter size, postnatal survival, pup body weights and body weight gains, anogenital distance, and areolae/nipple anlagen counts (male only) in the treated groups were unaffected.

Necropsy findings for F1 pups that died during PND 0-13 included a developmental variation that consisted of an accessory lobule in the liver in a pup in the 100 mg/kg bw/day group and a malformation that consisted of an interventricular septal defect (entire septum absent) in a pup in the control group. The study authors stated that no internal findings that could be attributed to parental test substance administration were noted at the necropsies of the pups there were found dead.

There were no treatment related changes in mean serum thyroxine (T4) levels or mean thyroid/parathyroid weights in F1 animals at the end of the treatment period.

Remarks – Results
Based on the absence of any treatment-related adverse effects at up to 1000 mg/kg bw/day, the No Observed Adverse Effect Level (NOAEL) for parental reproductive and systemic toxicity and F1 neonatal toxicity was established as the highest dose level tested.

CONCLUSION
The NOAEL for reproductive toxicity, neonatal toxicity and systemic toxicity was established as 1000 mg/kg bw/day, the highest dose tested, based on the absence of treatment-related adverse effects.

TEST FACILITY	WIL (2016)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test 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 - 5000 µg/plate b) Without metabolic activation: 50 - 5000 µg/plate
Vehicle	Tetrahydrofuran
Remarks - Method	GLP Certificate The dose selection for the main test (the dose-range study was reported as Test 1) was based on toxicity observed in the range-finding study carried out at 1.5-5000 µg/plate. Positive controls: With metabolic activation: 2-aminoanthracene (TA1535, TA1537, TA100); benzo(a)pyrene (TA98) Without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine (WP2uvrA, TA100, TA1535); 9-aminoacridine (TA1537); 4-nitroquinoline-1-oxide (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	> 5000		≥ 500	negative
Test 2		> 5000	≥ 500	negative
Present				
Test 1	> 5000		≥ 500	negative
Test 2		> 5000	≥ 500	negative

Remarks - Results

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any concentration tested, 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

Envigo (2015i)

B.8. Genotoxicity – *in vitro*

TEST SUBSTANCE

Analogue chemical (identity is exempt information)

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test

Species/Strain: Human

Cell Type/Cell Line: Peripheral lymphocytes

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

Vehicle: acetone

Remarks - Method: GLP Certificate

The dose selection for the main experiments was based on the lowest precipitation dose level observed in the range-finding study carried out at 0.625 – 160 µg/mL.

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

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	1.25, 2.5, 5, 10*, 20*, 30*, 40*	4 h	24 h
Test 2	1.25, 2.5, 5, 10*, 20*, 30*, 40*	24 h	24 h
Present			
Test 1	1.25, 2.5, 5, 10*, 20*, 30*, 40*	4 h	24 h

* Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 5*	≥ 40	negative
Test 2	> 20*	≥ 40	negative
Present			
Test 1	> 10*	≥ 40	negative

* It was stated in the report that the reductions in mitotic index were inconsistent throughout the dose ranges. They were not obviously dose related and may therefore be due to normal biological variation.

Remarks - Results	No statistically significant increases in the frequency of cells with chromosome aberrations were observed in the presence or absence of metabolic activation. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The test substance was not clastogenic to human peripheral lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	Envigo (2015j)

B.9. Genotoxicity – *in vitro*

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 476 *In Vitro* Mammalian Cell Gene Mutation Test
Species/Strain	Mouse
Cell Line	Lymphoma L5178Y cells
Metabolic Activation System	S9 mix from phenobarbital/β-naphtha flavone induced rat liver
Vehicle	Acetone
Remarks - Method	GLP Certificate The dose selection for the main test was based on toxicity observed in the range-finding study carried out at 4.88 - 1250 µg/mL. The positive controls used were ethyl methane sulphonate in the absence of metabolic activation and cyclophosphamide in the presence of metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*
Absent			
Test 1	19.53, 39.06, 78.13*, 156.25*, 312.5*, 625*,937.5*, 1250*	4 h	2 d
Test 2	19.53, 39.06, 78.13*, 156.25*, 312.5*, 625*,937.5*, 1250*	24 h	2 d
Present			
Test 1	19.53, 39.06, 78.13*, 156.25*, 312.5*, 625*,937.5*, 1250*	4 h	2 d

*Cultures selected for mutant frequency 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	> 1250	> 1250	≥ 78.13	Negative
Test 2	≥ 1250	≥ 1250	≥ 78.13	Negative
Present				
Test 1	> 1250	> 1250	≥ 78.13	Negative

* It was stated in the report that maximum dose levels were selected using the criteria i) maximum recommended dose level, 5000 µg/mL or 10 mM; ii) the presence of excessive precipitate where no test item-induced toxicity observed; and iii) test item-induced toxicity, where the maximum dose level used, should produce 10 - 20% survival.

Remarks - Results	The test substance was non-toxic and did not induce any toxicologically significant increases in the mutation frequency at any of the test concentrations, 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 mouse lymphoma L5178Y cells treated in vitro under the conditions of the test.
TEST FACILITY	Envigo (2015k)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test EC Council Regulation No 440/2008 C.4-C Ready Biodegradability US EPA Fate, Transport and Transformation Test Guidelines OCSPP 835.3110
Inoculum	Activated sludge from a STP
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	CO_2 by Tekmar-Dohrmann Apollo 9000 TOC Analyser or Shimadzu TOC analyser
Remarks - Method	No significant deviations from the test guidelines were reported. The test substance was dispersed directly in mineral medium. A toxicity control was run.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
2	13	2	42
10	43	10	82
28	57	28	104
29	53	29	84

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 60% within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 53%.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	Envigo (2015l)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish – Semi-static
Species	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography Flame Ionisation Detector (GC-FID)
Remarks – Method	No significant deviations from the test guidelines were reported. Due to the low aqueous solubility and complex nature of the test substance, the test medium was prepared as a Water Accommodated Fraction (WAF). The test substance was added to the surface of the test medium to give a

loading rate of 100 mg/L, followed by stirring by magnetic stirrer for 23 hours. The mixture was then allowed to stand for 1 hour, and the aqueous phase or WAF was removed by mid-depth siphoning to give the 100 mg/L loading rate WAF. Microscopic inspection of the WAF showed no micro-dispersions or undissolved test substance. For the duration of the test, the test medium was observed to be a clear and colourless solution. The concentration of the test substance was verified by chemical analysis at 0, 24, 72 and 96 hours. The test water was renewed daily. During the test, dissolved oxygen was ≥ 8.1 mg/L at 14°C (≥ 79% saturation; USGS 2011).

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
Control	Control	7	0
100	≤ 2	7	0

LC50 > 100 mg WAF/L at 96 hours

Remarks – Results All validity criteria for the test were satisfied.

CONCLUSION The test substance is not harmful to fish up to its water solubility limit.

TEST FACILITY Envigo (2015m)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Analogue chemical (identity is exempt information)

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 Gas Chromatography Flame Ionisation Detector (GC-FID)
Remarks - Method No significant deviations from the test guidelines were reported. Due to the low aqueous solubility and complex nature of the test substance, the test medium was prepared as a Water Accommodated Fraction (WAF). The test substance was added to the surface of the test medium to give a loading rate of 100 mg/L, followed by stirring by magnetic stirrer for 23 hours. The mixture was then allowed to stand for 1 hour and the aqueous phase or WAF was removed by mid-depth siphoning to give the 100 mg/L loading rate WAF. Microscopic inspection of the WAF showed no micro-dispersions or undissolved test substance. For the duration of the test, the test medium was observed to be a clear and colourless solution. The concentration of the test substance was verified by chemical analysis at 0 and 48 hours. During the test, dissolved oxygen was around 8.8 mg/L at 22°C (about 100% saturation; USGS 2011).

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*
Nominal	*Actual*		*48 h*
Control	Control	20	0
100	≤1.72	20	1*

*considered due to natural cause

LC50	> 100 mg WAF/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied.
CONCLUSION	The test substance is not harmful to aquatic invertebrates up to its water solubility limit.
TEST FACILITY	Envigo (2015n)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: ≤ 1.5 mg/L
Auxiliary Solvent	None
Water Hardness	Not determined
Analytical Monitoring	Gas Chromatography Flame Ionisation Detector (GC-FID)
Remarks - Method	No significant deviations from the test guidelines were reported. Due to the low aqueous solubility and complex nature of the test substance, the test medium was prepared as a Water Accommodated Fraction (WAF). The test substance was added to the surface of test medium to give a loading rate of 100 mg/L, followed by stirring by magnetic stirrer for 23 hours. The mixture was then allowed to stand for 1 hour, given the presence of dispersed test substance in the media column, it was considered appropriate to remove the aqueous phase by filtration through a glass wool plug. Microscopic examination of the WAF after filtration showed no micro-dispersions of test substance present. At the start of the test, all control and 100 mg/L loading rate WAF test cultures were observed to be clear colourless solutions. The concentration of the test substance was verified by chemical analysis at 0 and 72 hours.

RESULTS

Biomass		*Growth*	
EC50 *mg WAF/L at 48 h*	*NOEC* *mg WAF/L*	*EC50* *mg WAF/L at 48 h*	*NOEC* *mg WAF/L*
> 100	≥ 100	> 100	≥ 100

Remarks - Results	The mean cell density in the control increased by 113 times. All validity criteria for the test were satisfied.
CONCLUSION	The test substance is not harmful to aquatic invertebrates up to its water solubility limit.
TEST FACILITY	Envigo (2015o)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Analogue chemical (identity is exempt information)
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test
Inoculum	Activated sludge from a local STP
Exposure Period	3 hours
Concentration Range	Nominal: 10, 100, 1,000 mg/L

Remarks – Method	No significant deviations from the test guidelines were reported. The test substance was dispersed directly in test water and subjected to ultrasonication for 15 minutes followed by magnetic stirring for 24 hours in order to maximise the dissolved test substance concentration before starting the test. All test vessels were shielded during mixing. The dissolved oxygen concentrations after 30 minutes contact time in all vessels were above 60 to 70% of the dissolved oxygen saturation level of 8.9 mg O_2/L.
RESULTS	
IC50	> 1,000 mg/L
Remarks – Results	The validity criteria for the test were satisfied. In some instances, the initial and final dissolved oxygen concentrations were outside those recommended in the test guidelines (7 mgO_2/L and 2 mgO_2/L, respectively). This was considered to have had no adverse effect on the results of the study given that in all cases, the oxygen consumption rate was determined over the linear portion of the respiration curve.
CONCLUSION	The test substance does not inhibit microbial activity in STPs.
TEST FACILITY	Harlan (2015)

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