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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

TS 15021

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/1625	Cintox Australia Pty Ltd	TS 15021	ND*	≤ 500 tonnes per annum	Component of engine oils

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information on analogues, 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
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

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

Environmental risk assessment
On the basis of the assessed use pattern and low hazard, 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 isolation and engineering controls to minimise occupational exposure to the notified chemical during reformulation:
  - Enclosed, automated processes, where possible
  - Sufficient ventilation

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

- 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:
  - Coveralls
  - Impervious gloves
  - Eye protection
  - Respiratory protection if exposure to oil mists is expected

  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 containment, physical 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
  - toxicological information on skin sensitisation and repeated dose for the notified chemical becomes available;
  - the notified chemical is used in engine oils at concentrations > 1%;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of engine oils, 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 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)
Cintox Australia Pty Ltd (ABN: 63 122 874 613)
Suite 1, Level 2, 38-40 George Street
PARRAMATTA NSW 2150

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, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants, use details and identities of analogues.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for adsorption/desorption, dissociation constant, flammability, autoignition temperature and all toxicological and ecotoxicological endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
United States, European Union and Philippines

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
TS 15021 (contains > 60% notified chemical in solvents)

MOLECULAR WEIGHT
~ 500 Da (average)

ANALYTICAL DATA
Reference NMR and GPC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 60% as manufactured (contains solvents)

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: light brown liquid*

Property	Value	Data Source/Justification
Pour Point*	123 °C	Measured
Boiling Point*	> 222 °C	Measured
Density*	937.2 kg/m^3 at 20 °C	Measured
Vapour Pressure*	4×10^{-7} kPa at 20 °C	Measured
Water Solubility	2.2×10^{-4} g/L at 25 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functionalities.
Partition Coefficient (n-octanol/water)	log Pow = 8.09	Measured; expected to partition to phase boundaries based on surface activity.
Adsorption/Desorption	Not determined	Expected to adsorb to soil and sediment based on its surface activity.
Dissociation Constant	Not determined	Expected to be ionised under

		environmental conditions (pH 4-9)
Flash Point*	172 °C	Measured
Flammability	Not determined	Not expected to be flammable based on the measured flash point
Autoignition Temperature	Not determined	Estimated to be > 200 °C by the notifier
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

* Property of TS 15021 (contains > 60% notified chemical in solvents)

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties of TS 15021, 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 either as a component of lubricant additive packages (at ≤ 20% concentration) for reformulation into engine oils or as a component of finished engine oils (at ≤ 1% concentration).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	250	300	350	425	500

PORT OF ENTRY
Sydney, Melbourne, Fremantle and Brisbane

TRANSPORTATION AND PACKAGING
Lubricant additive packages and finished engine oils containing the notified chemical will be imported into Australia either in 20,000 L isotanks or in drums (such as 205 L steel drums) and then transported locally by road and by rail.

USE
The notified chemical will be used as a lubricating additive in engine oils at ≤ 1% concentration for marine vessels. Engine oils containing the notified chemical will be primarily used in industrial and commercial applications with a small portion available for do-it-yourself (DIY) use.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. The imported additive packages containing the notified chemical (at ≤ 20% concentration) will be reformulated into engine oils after importation and the imported finished engine oils will be directly used by professional or DIY end-users.

Reformulation
At the customers' facilities, it is expected that the additive packages containing the notified chemical at ≤ 20% concentration will be transferred into blending tanks using automated, enclosed and well-ventilated processes. After blending, it is expected that the end-use product containing the notified chemical at ≤ 1% concentration will be packaged into isotanks or drums using automated processes. The resulting engine oil products will be supplied to industrial and commercial end-users, and possibly to retail stores.

End-use
Engine oil products containing ≤ 1% notified chemical will be primarily used at industrial and commercial sites such as marine vessel manufacture and maintenance sites where the engine oils are expected to be added to the lubricating oil reservoir from isotanks or drums by piping when used in stationary engines or using pneumatic delivery equipment when used in non-stationary marine applications. Engine oil products containing ≤ 1% notified chemical may also be used by DIY users via manual transfer. The engine oils will remain in the engines until next oil change. Used oils will be captured for recycling or disposal.

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)*
Unloading isotanks and drums of additive packages	0.5	30
Sampling and analysing additive packages	0.2	220
Unloading isotanks and drums of finished oils	0.5	30
Sampling and analyzing finished oils	0.2	220
Loading oilsinto tank trucks	0.5	220
Distribution to service stations	0.5	220
Mechanics/Engineers	8	12

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical at ≤ 20% concentration in either the imported or the end-use products only in the unlikely event of accidental rupture of containers.

Reformulation
Dermal and ocular exposure of workers to the notified chemical (at ≤ 20% concentration) may occur when connecting and disconnecting hoses and during sample testing. The exposure should be limited as the blending and packaging processes are expected to be automated and within a closed system.

Dermal and ocular exposure to workers should be further mitigated through the use of personal protective equipment (PPE) including protective clothing, impervious gloves and safety glasses, as anticipated by the notifier. Although oil mists may be generated, exposure is expected to be limited due to the enclosed nature of the blending and repackaging operations and sufficient ventilation.

End-use
At marine vessel manufacture and maintenance sites, professional users such as mechanics may experience dermal or ocular exposure to the engine lubricant products containing the notified chemical at ≤ 1% concentration when transferring engine oils to engines of marine vessels. The potential for dermal and ocular exposure may be mitigated through the use of PPE. Inhalation exposure is not expected given that respirable oil mists are not likely to be generated due to the low vapour pressure the notified chemical and high viscosity of the finished oils.

6.1.2. Public Exposure
Engine oils containing the notified chemical may be manually transferred between the container and the lubricating oil reservoir by DIY users. Similar to professional end-users, dermal and ocular exposure to the notified chemical at ≤ 1% concentration may occur; however it is expected to be of low frequency. It is not known whether PPE would be used by DIY users during oil transfer, however, DIY users are expected to avoid oil splashes, and wash off any spills from the skin.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on analogues of 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 > 5004 mg/kg bw; low toxicity
Rat, acute dermal toxicity*	LD50 > 2006 mg/kg bw; low toxicity
Rabbit, skin irritation*	slightly irritating
Rabbit, eye irritation*	slightly irritating
Guinea pig, skin sensitisation – non-adjuvant test*	evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay*	evidence of sensitisation
Human, skin sensitisation – RIPT (up to 100%)*	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days[#]	NOAEL > 1000 mg/kg bw/day (male) NOAEL = 500 mg/kg bw/day (female)
Mutagenicity – bacterial reverse mutation*	non mutagenic
Genotoxicity – in vivo micronucleus assay*	non genotoxic
Rat, reproductive toxicity[#]	NOAEL > 500 mg/kg bw/day

* Test substance was Analogue 1 (identity in Exempt Information).
[#] Test substance was Analogue 4 (identity in Exempt Information).

Toxicokinetics
Based on the molecular weight (average ~ 500 Da) of the notified chemical, there is potential for the chemical to cross biological membranes. However, absorption may be limited based on the water solubility (2.2×10^{-4} g/L at 25 °C) and partition coefficient (log Pow = 8.09) of the notified chemical.

Acute toxicity
No acute toxicity data were submitted for the notified chemical. Analogue 1 was found to be of low toxicity via the oral and dermal routes in studies conducted in rats. No inhalation toxicity data was provided.

Irritation
No irritation data were submitted for the notified chemical. In studies conducted in rabbits, Analogue 1 was found to be slightly irritating to the skin and eyes.

Sensitisation
No sensitisation data were submitted for the notified chemical. Analogue 1 caused skin sensitisation in a guinea pig maximisation study (treated animals had higher incidence and severity of irritation compared to the control animal) and in a local lymph node assay (EC3 < 25%) but was negative in a human repeat insult patch test with 101 subjects who completed the test (tested at 100% concentration).

Multiple animal and human studies on lower molecular weight analogues showed negative results for skin sensitisation (OECD 2005, HERA 2013).

Submitted QSAR modelling using OASIS–TIMES (v. 2.28.1.4) with Autoxidation model (v. 22.27) predicted negative results for skin sensitisation for Analogue 2 and 9 of its metabolites, indicating no structural alerts for skin sensitisation. Similar modelling submitted on the 90 constituents that comprise Analogue 3 and the metabolites of these constituents indicated that all were predicted to be non-sensitising.

Based on weight of evidence, the notified chemical is not classified as a skin sensitiser but the potential for sensitisation effects cannot be ruled out.

Repeated dose toxicity
No repeated dose toxicity data were submitted for the notified chemical. A repeated dose oral (gavage) toxicity study on Analogue 4 was conducted in rats, in which the test substance was administered at 50, 150, 500 and 1000 mg/kg bw/day for 28 consecutive days, with a 14-day recovery period for high dose and control animals.

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day for males in this study, as all treatment-related changes were either of no toxicological significance or non-adverse due to their reversibility by the end of the recovery period.

The NOAEL was established as 150 mg/kg bw/day for females in this study, based on an ulcer with inflammation, hyperplasia, haemorrhage and oedema was noted in the stomach of 1 female at 500 mg/kg bw/day.

Mutagenicity/Genotoxicity
No mutagenicity/genotoxicity data were submitted for the notified chemical. Analogue 1 was negative in a bacterial reverse mutation assay and in an *in vivo* mouse micronucleus assay.

Toxicity for reproduction
No reproductive toxicity data were submitted for the notified chemical. In an oral one-generation reproductive study, Analogue 4 was administered to rats at doses of 50, 167 or 500 mg/kg bw/day. The most remarkable findings in the study were a slight, but dose-responsive increase in post-dose observations of salivation and dark material around the nose for the parental male animals.

The NOAEL was established as 500 mg/kg bw/day, based on the absence of toxicologically significant, treatment-related effects at up to the highest dose level.

Health hazard classification
Based on the available information on analogues, 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
Significant systemic toxicity is not expected based on the submitted analogue data and predicted limited absorption across biological membranes. The potential for skin sensitisation cannot be ruled out based on the mixed results from tests and modelled data on analogues.

There is potential for dermal and ocular exposure of workers to the notified chemical at ≤ 20% concentration during reformulation processes. Exposure should be minimised through the use of enclosed, automated processes, sufficient ventilation and PPE. There is also potential for dermal and ocular exposure of workers to the notified chemical at ≤ 1% concentration during transfer of engine oils containing the notified chemical between containers and engine oil reservoirs. Such exposure is expected to be mitigated through the use of automated processes and/or PPE.

Overall, provided engineering controls are instituted during reformulation, workers wear appropriate PPE, and safe work practices are maintained to reduce exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health
The potential for dermal and ocular exposure of DIY users to the notified chemical at up to 1% is expected during transferring engine oils containing the notified chemical between containers and engine oil reservoirs. However, the risk to the DIY users from use of the notified polymer is not considered to be unreasonable given the low end-use concentrations and expected low use frequency.

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 a component of lubricant additive packages for reformulation into engine lubricant oils, or as a component of finished engine lubricant oils. No significant release of the notified chemical is expected from transportation and storage, except in the unlikely event of accidental spill and leaks.

Local blending of the additive containing the notified chemical into lubricants is expected to occur within enclosed automated systems. The finished product will be transferred back to the storage tanks and from their filled into drums or isotainers. Empty import drums will be steamed cleaned, and the wastes containing the notified chemical will be collected for disposal in accordance with local government regulations or by licensed waste management services. It is estimated by the notifier that 0.1% of the annual import volume (500 kg) of the notified chemical may be sent to the waste water treatment facilities.

RELEASE OF CHEMICAL FROM USE

The finished products containing the notified chemical will be mainly used as a component of lubricating oil additive at industrial and commercial sites such as marine vessel manufacture and maintenance sites. Release during use may arise from spills when pouring lubricants into engines or from engine leaks, and is expected to be very low.

It is estimated by the notifier that 15% of lubricant products containing the notified chemical will be used by do-it-yourself (DIY) consumers. According to a survey tracing the fate of used lubricating oil in Australia (Snow, 1997), approximately 20% of oil used by DIY consumers is collected for recycling, 25% is buried or disposed of to landfill, 5% is disposed of into stormwater drains, and the remaining 50% is used in treating fence posts, killing grass and weeds or disposed of in other ways. In a worst case scenario involving the 15% of oil used by DIY consumers, up to 0.75% (15% × 5% stormwater disposal) of the total import volume of the notified chemical (or 3,750 kg) may enter the aquatic environment via disposal to stormwater drains. Since the use of the engine oils will occur throughout Australia, all releases resulting from use or disposal of used oil will be very diffuse.

RELEASE OF CHEMICAL FROM DISPOSAL

Any spent or waste product containing the notified chemical is expected to be recycled, re-refined or used as low grade burner fuel, or disposed of by approved waste management. It is likely that the notified chemical will be degraded into simpler compounds during refining, with any residue partitioning to the heavy fractions such as lubricating oils or asphalt.

7.1.2. Environmental Fate

The notified chemical is not expected to be readily biodegradable based on the results of a biodegradability study conducted on analogue 6 (12.5% in 29 days). For details of environmental study, please refer to Appendix C. The majority of the notified chemical in engine oils will be either thermally decomposed during use or recycled. Notified chemical disposed of to landfill is not expected to be mobile or bioavailable based on its low water solubility and surfactant properties. The notified chemical is expected to have a low bioaccumulation potential based on the measured data of the analogue. In landfill, the notified chemical is expected to eventually degrade by biotic and abiotic processes to form water and oxides of carbon and sulphur and inorganic salts.

7.1.3. Predicted Environmental Concentration (PEC)

As a worst case scenario, the percentage of the imported quantity of notified chemical inappropriately disposed to stormwater drains is estimated to be 0.75% (that is, 15% fraction collected by DIY users × 5% fraction disposed to stormwater). The release of the notified chemical may be up to 3,750 kg/year (= 500 tonnes/year × 0.75%). In this worst case scenario, it is assumed that the release goes into stormwater drains in a single metropolitan area with a geographical footprint of 500 km^2 and an average annual rainfall of 500 mm, all of which drains to stormwater. With a maximum annual release into this localised stormwater system of 3,750 kg and the annual volume of water drained from this region estimated to be 250 × 10^6 m^3, the calculated PEC will be up to 15 µg/L. This result reflects a worst-case scenario upper limit, as in reality release of the notified chemical will be distributed over multiple regions and it will be further diluted if it reaches the ocean.

It is assumed by the notifier that 0.1 % of the total import volume of the notified chemical may be released to the waste water treatment facilities. The release is assumed to be nationwide over 365 days per year and there is no removal within sewage treatment plants (STPs) under a worst case scenario.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	500,000	kg/year
Proportion expected to be released to sewer	0.1%	
Annual quantity of chemical released to sewer	500	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	1.37	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	

PEC - River:	0.28	µg/L
PEC - Ocean:	0.03	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.28 µg/L may potentially result in a soil concentration of approximately 0.002 mg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 0.009 mg/kg and 0.019 mg/kg, respectively.

Based on the calculation above, the combined Predicted Environmental Concentration (PEC) in river will be

$$PEC_{river} = 15.00 \text{ µg/L} + 0.28 \text{ µg/L} = 15.28 \text{ µg/L}$$

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical and accepted analogues (Analogue 5 and 6) are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Acute toxicity*		
Fish Toxicity	96 h LL50 > 1000 mg/L (WAF¥)	Not harmful to fish up to the limit of its water solubility
Daphnia Toxicity	48 h EL50 > 1000 mg/L (WAF¥)	Not harmful to aquatic invertebrates up to the limit of its water solubility
Algal Toxicity	96 h EL50 > 1000 mg/L (WAF¥)	Not harmful to algae up to the limit of its water solubility
Chronic toxicity§		
Daphnia Toxicity	21 d NOEL > 100 mg/L (WAF¥)	Not harmful to aquatic invertebrates up to the limit of its water solubility

* Analogue data (identity in Exempt Information)
¥ Water Accommodated Fraction
§ The notified chemical, full study report was not provided

Based on the above ecotoxicological endpoints for the notified chemical and its analogues, it is not expected to be harmful to aquatic life up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated, since the notified chemical is not expected to be harmful to aquatic life up to the limit of its solubility in water. There is also no significant release of the notified chemical to the aquatic environment expected.

7.3. Environmental Risk Assessment

A Risk Quotient (RQ = PEC/PNEC) has not been calculated based on low hazard of the notified chemical. Although the notified chemical is not considered readily biodegradable, it is expected to have a low potential for bioaccumulation. On the basis of the assessed use pattern as a component of engine lubricant oils and the expected limited aquatic release, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Following physical-chemical properties were tested on TS 15021 containing > 60% notified chemical in solvents.

Melting Point/Freezing Point 123 °C

Method	ASTM D97.
Remarks	Determined by ASTM D97 after heating the test substance well above room temperature due to the test substance was extremely viscous at room temperature.
Test Facility	Exempt information (2016)

Boiling Point > 222 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Determined by vacuum thermogravimetric analysis
Test Facility	Exempt information (2016)

Density 937.2 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Determined by oscillating densitometer
Test Facility	Exempt information (2016)

Vapour Pressure 4×10^{-7} kPa at 20 °C (calculated)

Method	OECD TG 104 Vapour Pressure.
Remarks	API gravity and high temperature simulation distillation were used to calculate the vapour pressure by the Maxwell-Bonnell/ProVision method.
Test Facility	Exempt information (2016)

Water Solubility 0.22 mg/L at 25 °C

Method	OECD TG 105 Water Solubility.
Remarks	Determined by shake flask method
Test Facility	Exempt information (2016)

Partition Coefficient (n-octanol/water) log Pow = 8.09

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	Determined by HPLC Method
Test Facility	Exempt information (2016)

Flash Point 172 °C

Method	ASTM D93.
Remarks	Determined by Pensky-Martens Closed Cup Tester
Test Facility	Exempt information (2016)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Analogue 1 (identity in Exempt Information)

METHOD: OECD TG 401 Acute Oral Toxicity – Limit Test.
- Species/Strain: Rat/Sprague-Dawley
- Vehicle: None
- Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5F	5004	0/5
2	5M	5004	0/5

- LD50: > 5004 mg/kg bw
- Signs of Toxicity: No abnormal clinical signs were noted.
- Effects in Organs: No treatment-related macroscopic findings were noted at necropsy.
- Remarks - Results: All animals showed expected body weight changes.

CONCLUSION: The test substance is of low toxicity via the oral route.

TEST FACILITY: Pharmakon (1997a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Analogue 1 (identity in Exempt Information)

METHOD: OECD TG 402 Acute Dermal Toxicity – Limit Test.
- Species/Strain: Rat/ Sprague-Dawley
- Vehicle: None
- Type of dressing: Semi-occlusive
- Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5F	2006	0/5
2	5M	2006	0/5

- LD50: > 2006 mg/kg bw
- Signs of Toxicity - Local: No erythema or oedema was noted.
- Signs of Toxicity - Systemic: No abnormal clinical signs were noted.
- Effects in Organs: No treatment-related macroscopic findings were noted at necropsy.
- Remarks - Results: There were no treatment-related effects on body weight.

CONCLUSION: The test substance is of low toxicity via the dermal route.

TEST FACILITY: Pharmakon (1997b)

B.3. Irritation – skin

TEST SUBSTANCE: Analogue 1 (identity in Exempt Information)

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion.
- Species/Strain: Rabbit/New Zealand White

Number of Animals	6
Vehicle	Test substance administered as supplied
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Erythema/Eschar	0	0.3	0.3	0	0	0.3	1	< 72 h	0
Oedema	0	0	0	0	0	0	0	-	0

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

Remarks - Results	No mortality was noted. Very slight to slight erythema was noted in all animals at the 1-hour observation. Very slight erythema was noted in 2 animals at the 24 hour observation and 1 animal at the 48-hour observation. No oedema was noted.

CONCLUSION The test substance is slightly irritating to the skin.

TEST FACILITY Pharmakon (1997c)

B.4. Irritation – eye

TEST SUBSTANCE Analogue 1 (identity in Exempt Information)

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (rinsed) and 6 (non-rinsed)
Observation Period	7 days
Remarks - Method	No significant protocol deviations. Rinsed group: the lower and upper eyelids were held in contact for 30 seconds to prevent loss of the test substance. Non-rinsed group: the test substance was left in contact with the eye for 30 seconds and then rinsed for 30 seconds with tepid tap water.

RESULTS

Group 1 (rinsed)

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	1	1.3	0.3	2	< 7 days	0
Conjunctiva: chemosis	0	0	0	1	< 24 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	1	< 24 hours	0

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

Group 2 (non-rinsed)

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Conjunctiva: redness	0.3	1.7	0.3	0.3	0.3	1.3	2	< 7 days	0

Conjunctiva: chemosis	0	0	0	0	0	0	1	< 24 hours	0
Corneal opacity	0	0	0	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	0	0	1	< 24 hours	0

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

Remarks - Results

No mortality was noted.

Slight chemosis and moderate reddening of the conjunctivae was noted in all animals at the 1-hour observation. All animals continue to show slight to moderate reddening of the conjunctivae at the 24-hour observation and slight reddening persisted in 2 animals at the 48 and 72-hour observations in both groups. Slight iridial inflammation was noted in 1/3 of the animals in either group at the 1-hour observation.

All effects were fully resolved at Day 7 observation.

CONCLUSION

The test substance is slightly irritating to the eye.

TEST FACILITY

Pharmakon (1997d)

B.5. Skin sensitisation

TEST SUBSTANCE

Analogue 1 (identity in Exempt Information)

METHOD

OECD TG 406 Skin Sensitisation - Buehler Test.

Species/Strain

Guinea pig/Hartley albino

PRELIMINARY STUDY

Maximum Non-irritating Concentration:
topical: 0.5%

MAIN STUDY

Number of Animals

Test Group: 20 Control Group: 10

Vehicle

Spectrum mineral oil light

Positive control

Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 1-chloro-2,4-dinitrobenzene.

INDUCTION PHASE

Induction Concentration:
topical: 100%

Signs of Irritation

Not reported

CHALLENGE PHASE

challenge

topical: 50%

Remarks - Method

In the preliminary study, only mild irritation was noted at up to 100% concentration. Therefore, this concentration was selected for use at induction in the main study.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	50%	15/19	15/19
Control Group (vehicle)	50%	2/10	4/10

Remarks - Results

At the 24 h observation, mean severity score for the test group and control group were 1.1 and 0.6 respectively.

At the 48 h observation, mean severity score for the test group and control group were 1.3 and 0.7 respectively.

A male animal in the test group was found dead on the challenge date. Observations on the deceased rat included dark and mottled lungs and pale and mottled liver. A clear red bloud like substance was observed around the nose and mouth.

CONCLUSION	There was evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.
TEST FACILITY	Hill top (1991)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Analogue 1 (identity in 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	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method	No significant protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5F	709.14	-
25%	5F	5,533.22	7.8
50%	5F	10,971.63	15.47
100%	5F	8,746.31	12.33

EC3	< 25%
Remarks - Results	In the preliminary study, there were no signs of systemic toxicity noted. In the main study, there were no mortality or signs of systemic toxicity observed in the test or control animals. Mild redness to the head, neck and ears was noted for animals treated with the test substance at 50% concentration on Days 4 and 5 and for animals treated with the test substance at 100% concentration on Days 3-5. The auricular lymph nodes of the animals in control group were considered normal in size while the nodes of the animals in 25%, 50% and 100% concentration groups were considered enlarged. No macroscopic abnormalities of the surrounding area were noted for any animals. The test substance elicited a SI ≥ 3 and is therefore considered a skin sensitiser. All treated animals showed body weight changes comparable to those of the vehicle control group.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance at or above the minimum concentration (25%) tested.
TEST FACILITY	Harlan (2009)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Analogue 1 (identity in Exempt Information)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were

	applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday). Rest Period: 14 days Challenge Procedure: Patches identical to those applied at induction were applied to sites previously unexposed to the test substance. Patches were removed by the applicants after 24 hours and graded after additional 24 hours and 48 hours.
Study Group	101 F, 8 M; age range 21-60 years
Vehicle	Mineral oil
Remarks - Method	Occluded. The test substance was spread on a 2 cm × 2 cm patch.

RESULTS

Remarks - Results	The test substance was tested at concentrations of 10%, 25%, 50% and 100% in the pilot phase of the study (19/20 subjects completed). Concentration of 100% was selected for the main study, based on the results from the pilot study. 101/109 subjects completed the study. No withdrawals were related to the application of the test substance. No clinically significant irritation was noted following the challenge.

CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (1992)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Analogue 4 (identity in Exempt Information)
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	
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	Corn oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	50	0/10
mid dose 1	5 per sex	150	0/10
mid dose 2	5 per sex	500	0/10
high dose	5 per sex	1000	0/10
control recovery	5 per sex	0	0/10
high dose recovery	5 per sex	1000	0/10

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

No significant clinical abnormalities or toxicologically significant neurological changes were noted.

Body weight effects were primarily noted in male animals of the 500 mg/kg bw/day and 1000 mg/kg bw/day dose groups, including decreased weight gain (both groups) and food consumption (500 mg/kg bw/day dose

group) during week 3 and remained lower than the control group by the end of the treatment (both groups) and by the end of the recovery (1000 mg/kg bw/day dose group).

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology and coagulation
Increased platelet counts, eosinophils, basophils and mean corpuscular haemoglobin concentration were noted in male animals of the ≥ 150 mg/kg bw/day dose groups. However, these findings were not considered by the study authors to be toxicologically significant or relevant due to no dose-response relationship, no correlative changes in other haematology parameters or the change only occurred at the end of the recovery.

No statistically significant or notable changes in haematology parameters were noted in female animals.

Clinical chemistry
Increased gamma-glutamyl transferase, serum alanine aminotransferase, serum phosphorus and bilirubin were noted in male animals of all dose groups. However, these changes were not considered by the study authors to be toxicologically significant or relevant due to a single incident, no dose-response relationship or the lack of correlative microscopic changes or the lack of correlative changes in related haematology parameters.

No statistically significant or notable changes in clinical chemistry parameters were noted in male animals at the end of recovery.

Increased alanine aminotransferase and decreased sodium and chloride were noted in female animals of the 1000 mg/kg bw/day dose and 500 mg/kg bw/day dose groups. However, these changes were considered by the study authors to be of questionable toxicological significance or not toxicologically significant due to the lack of correlative microscopic changes, the lack of correlative changes in other chemical chemistry parameters or no dose-response relationship.

Urinalysis
Decreased urine pH was noted in male animals of the 1000 mg/kg bw/day dose group. However, this change was not considered by the study authors to be toxicologically significant as it occurred only at the end of the recovery phase and there was a lack of correlative microscopic changes in the kidney.

No statistically significant or toxicologically significant changes in urinalysis parameters were noted in female animals.

Effects in Organs

Organ weights
Changes in spleen, liver, thymus and adrenal weights were not considered by the study authors to be toxicologically significant due to the absence of any microscopic pathology, the lack of a clear dose-response in the spleen and adrenal findings and the lack of meaningful changes in liver enzymes examined.

Histopathology
Minimal oedema in the submucosa was noted in 2/5 male animals of the 500 mg/kg bw/day dose group. Minimal to mild oedema in the submucosa and minimal epithelial hyperplasia were noted in 3/5 male animals of the 1000 mg/kg bw/day dose group.
Minimal oedema in the submucosa was noted in 2/5 female animals of the 150 mg/kg bw/day dose group. Mild oedema in the submucosa, minimal haemorrhage, minimal epithelial hyperplasia, mild inflammation and a mild ulcer were noted in 1/5 female animal of the 500 mg/kg bw/day dose group. Mild oedema in the submucosa (1/5) and minimal to mild epithelial hyperplasia (2/5) were also noted in the 1000 mg/kg bw/day dose group.

Remarks – Results
No mortality, notable clinical, neurological or clinical pathology abnormalities were noted at up to 1000 mg/kg bw/day. Microscopic findings of minimal irritation of the non-glandular portion of the stomach were noted in male animals at 500 mg/kg bw/day and 1000 mg/kg bw/day but limited to mild oedema and minimal hyperplasia which were resolved by the end of recovery. Minimal irritation of the non-glandular portion of the stomach was noted in female animals at 150 mg/kg bw/day and 1000 mg/kg bw/day and resolved by the end of recovery. However, an ulcer with inflammation, hyperplasia, haemorrhage and oedema was noted in the stomach of 1 female at 500 mg/kg bw/day.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day for males in this study, based on all treatment-related changes were either of no toxicological significance or non-adverse due to their reversibility by the end of the recovery period.

The NOAEL was established as 150 mg/kg bw/day for females in this study, based on an ulcer with inflammation, hyperplasia, haemorrhage and oedema was noted in the stomach of 1 female at 500 mg/kg bw/day.

TEST FACILITY Springborn (2003)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE Analogue 1 (identity in Exempt Information)

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from Aroclor induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 100-10,000 µg/plate b) Without metabolic activation: 100-10,000 µg/plate
Vehicle	Pluronic F127 (25% w/w in ethanol)
Remarks - Method	The selection of doses used in the main study was based on the results of a preliminary study. Positive controls: With metabolic activation: 2-aminoanthracene (TA1535, TA1537, TA100, WP2uvrA); benzo(a)pyrene (TA98) Without metabolic activation: 2-nitrofluorene (TA98); sodium azide (TA100, TA1535); ICR-191 (TA1537); 4-nitroquinoline-1-oxide (WP2uvrA)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 10,000	> 10,000	≥ 5,000	negative
Test 2		> 10,000	≥ 5,000	negative
Present				
Test 1	> 10,000	> 10,000	≥ 1,000	negative
Test 2		> 10,000	≥ 5,000	negative

Remarks - Results No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION The test substance was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY Corning Hazleton (1997)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE	Analogue 1 (identity in Exempt Information)
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/Crl:CD-1(ICR) BR
Route of Administration	Intraperitoneal administration
Vehicle	Peanut oil
Remarks - Method	A dose range-finding study was carried out at 1625-5000 mg/kg. The selection of doses used in the main study was based on the results of the preliminary study. Toxicity was indicated by the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) and mutagenic response was indicated by the relevant increase of micronucleated PCEs.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
Ia (vehicle control)	5 per sex	0	24
Ib (vehicle control)	5 per sex	0	48
Ic (vehicle control)	5 per sex	0	72
IIa (low dose)	5 per sex	625	24
IIb (low dose)	5 per sex	625	48
IIc (low dose)	5 per sex	625	72
IIIa (mid dose)	5 per sex	1250	24
IIIb (mid dose)	5 per sex	1250	48
IIIc (mid dose)	5 per sex	1250	72
IVa (high dose)	5 per sex	2500	24
IVb (high dose)	5 per sex	2500	48
IVc (high dose)	5 per sex	2500	72
V (positive control, CP)	5 per sex	10 mL/kg bw	24

CP=cyclophosphamide

RESULTS	
Doses Producing Toxicity	At the 24 h harvest time, animals in the low and mid dose groups were normal and animals in the high dose group were slightly hypoactive. At the 48 h harvest time, animals in the low dose group were normal and male animals in the mid dose group were slightly hypoactive with rough haircoats (female animals were normal). 1 animal in the high dose group was found dead and remaining animals were hypoactive with rough haircoats (1 male animal was very hypoactive with very rough haircoats, tremors and laboured breathing). At the 72 h harvest time, animals in the low dose group were slightly hypoactive and animals in the mid dose group were hypoactive with rough haircoats. An extra animal in the high dose group was found dead and remaining animals were hypoactive with rough haircoats, laboured breathing and distended abdomens.
Genotoxic Effects	There were no statistically significant increases in the frequency of micronucleated PCEs.
Remarks - Results	Bone marrow cytotoxicity was noted at 2500 mg/kg, although it was unclear whether the test substance was cytotoxic to the bone marrow at 625 mg/kg and 1250 mg/kg. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The test substance was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.

TEST FACILITY Corning Hazleton (1996)

B.11. Toxicity to reproduction – one generation study

TEST SUBSTANCE Analogue 4 (identity in Exempt Information)

METHOD OECD TG 415 One-Generation Reproduction Toxicity Study.
Species/Strain Rat/Crl:CD(SD)IGS BR
Route of Administration Oral – gavage
Exposure Information Exposure period - female: minimum 14 days prior to mating until lactation Day20
Exposure period - male: minimum 70 days prior to mating and until parturition completion
Vehicle Corn oil
Remarks – Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
1	28 per sex	0	2/90
2	28 per sex	50	0/70
3	28 per sex	167	1/70
4	28 per sex	500	2/90

Mortality and Time to Death
All parental male animals survived to scheduled euthanasia. Three parental females (1 in Group 3 and 2 in Group 4) were euthanised on gestation day 25 as they showed positive evidence of copulation after mating, but failed to deliver. These female animals were found to be non-pregnant and these findings were not considered by the study authors to be toxicologically meaningful as the parental reproductive indices appeared unaffected by the treatment at up to 500 mg/kg bw/day.

Effects on Parental (P) animals:

Clinical observations
A dose-related increase in post-dose salivation and dark material around the nose was noted for 12 treated male animals. Only three treated female animals showed post-dose salivation at the high-dose level.

Body weight and body weight changes
There were no statistically significant differences in body weight or body weight change for treated male animals from days 0-105 (prior to, during and after mating), with one exception. Mean body weight change was showed a statistically significant increase during days 35-42 in Group 3 but the increase was not considered by the study authors to be toxicologically meaningful due to the lack of dose-response relationship.

No statistically significant differences in body weight or body weight change were noted in treated female animals prior to mating (days 0-14) or during gestation (gestation days 0-21).

Food consumption
Slight increases in mean food consumption were noted in some of the treated male animals during the dosing period and were not considered by the study authors to be toxicologically meaningful due to the lake of a consistent relationship to treatment and did not appear to have detrimental effects.

There were no statistically significant or toxicologically meaningful differences in food consumption for female animals prior to mating or during gestation.

Reproduction
Slightly decreased duration of gestation was noted in the Groups 2 and 4. An increased live-born index and a decreased still-born index were noted in Group 2. A decrease in mean pup weight/litter was noted in Group 2. However, these changes were not considered by the study authors to be toxicologically meaningful due to the

lack of an apparent dose-response relationship.

Gross necropsy observations
No toxicologically significant findings were noted for male animals. Negative ammonium sulphide staining was noted in 1 female animals of Group 3 and in 2 female animals of Group 4. The 3 female animals failed to deliver and were euthanised on gestation Day 25. No other toxicologically significant findings for were noted for female animals.

Organ weight
Mean epididymides weights were decreased in group 4 males, but not considered toxicologically relevant by the study authors as there were no corresponding histopathological effects. The remaining mean absolute organ weights and organ to body weight ratios were comparable among the groups and included the liver, kidneys, brain, prostate, testes and seminal vesicles.

No statistically significant differences in mean absolute organ (brain, liver and kidney) weight and organ to body weight ratio were noted in female animals.

Semen analysis
Sperm count, concentration, motility and morphology from all treated animals were comparable to the control.

Histopathology
No treatment-related microscopic lesions were noted.

Effects on 1st Filial Generation (F1)
Pup observations during lactation
No clinical signs of treatment-related changes during lactation Days 0-21.

Pup gross necropsy observations
No toxicological significant, treatment-related findings were noted.

Remarks - Results
The most remarkable findings in the study were a slight, but dose-responsive increase in post-dose observations of salivation and dark material around the nose for the parental male animals.

CONCLUSION
The NOAEL was established as 500 mg/kg bw/day in this study, based on the absence of toxicologically significant, treatment-related effects at any dose level.

TEST FACILITY Springborn (2004)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability (Analogue)

TEST SUBSTANCE	Analogue 6
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	The activated sludge
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Carbon Dioxide
Remarks - Method	The amount of evolved CO_2 from the biodegradation of the test substance was expressed as a percentage of the theoretical amount of CO_2 (TCO_2) that could have been produced if complete biodegradation of the test substance occurred. The test substance was added to the treatment test chambers by direct weight addition.

RESULTS

Test substance		*Canola oil*	
Day	*% TCO_2**	*Day*	*% TCO_2**
6	1.15	6	29.55
13	5.40	13	61.25
23	11.3	23	79.60
29	12.5	29	82.30

*Mean value based on two replicates

Remarks - Results	The percentage degradation of the reference compound surpassed the threshold level of 60% by 14 days indicating the suitability of the inoculums. However, one replicate showed lower biodegradation levels and was excluded from the calculation without any justification. The degree of degradation of the test substance after 29 days was 12.5%.
CONCLUSION	The analogue to the notified chemical is not readily biodegradable
TEST FACILITY	Wildlife International Ltd. (1998)

C.1.2. Bioaccumulation (Analogue)

TEST SUBSTANCE	Analogue 6
METHOD	OECD TG 305 Bioconcentration: Flow-through Fish Test.
Species	*Oncorhynchus mykiss* (rainbow trout)
Exposure Period	Exposure: 39 days Depuration: 61 days
Auxiliary Solvent	Dimethylformamide
Concentration Range	Nominal: 0.0010, 0.010 mg/L Actual: 0.00090-0.0015 (90-150% of nominal), 0.0080-0.014 (80-140% of nominal) mg/L
Analytical Monitoring	Liquid Scintillation Counting and High Performance Liquid Chromatography
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Based on the water solubility limits and the results of the test previously performed, the test was conducted at nominal concentrations of 0.001 and 0.01 mg notified chemical/L. Two solvent stock solutions of ^{14}C labelled test material in dimethylformamide (DMF) at a concentration of 1.05 mg/ml were used to

prepare stock solutions for the 0.001 mg/L and 0.01 mg/L concentrations. The solvent control group was exposed to 33.3 µl/L of DMF.

RESULTS

Bioconcentration Factor (whole fish)	BCF_{ss} = 45 at low concentration (0.001 mg/L) and BCF_{ss}=58 at higher concentration (0.01 mg/L) based on total radioactivity.
Bioconcentration Factor (head and viscera)	BCF_{ss} = 86 at low concentration (0.001 mg/L) and BCF_{ss}=95 at higher concentration (0.01 mg/L) based on total radioactivity.
Bioconcentration Factor (body)	BCF_{ss} = 25 at low concentration (0.001 mg/L) and BCF_{ss}=40 at higher concentration (0.01 mg/L) based on total radioactivity.
Kinetic Bioconcentration Factor	BCF_k = 38 at low concentration (0.001 mg/L) and BCF_k= 64 at higher concentration (0.01 mg/L) based on the uptake and depuration rate constants.
Remarks - Results	There were no sub-lethal effects of exposure observed at test concentrations of 0.001 and 0.01 mg/L. All validity criteria were met except the concentrations were outside the ± 20% of the mean of the measured values during the uptake phase on a single occasion for the 0.001 and 0.01 mg/L test concentrations. Steady state concentrations were reached after 35 days exposure. At the end of depuration period 70% and 97% of the test substance was eliminated from the fish tissues for the 0.001 and 0.01 mg/L test concentration, respectively

CONCLUSION Under the conditions of this test, the test substance is not considered to be bioaccumulative.

TEST FACILITY Harlan Laboratories Inc. (2010)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish (Analogue)

TEST SUBSTANCE Analogue 5

METHOD Modified OECD TG 203 Fish, Acute Toxicity Test – Semi-static.

Species	*Pimephales promelas*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	176 mg/L $CaCO_3$/L
Analytical Monitoring	Total organic carbon measurements
Remarks – Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for 1 hour and then the solution was siphoned into the test chamber. No insoluble material was observed in any test vessel.

RESULTS

Concentration WAF mg/L*		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
0 (1)	ND§	10	0	0	0	0
0 (2)	ND	10	0	0	0	0
100 (1)	ND	10	0	0	0	0
100 (2)	ND	10	0	0	0	0
300 (1)	ND	10	0	0	0	0
300 (2)	ND	10	0	0	0	0

1,000 (1)	ND	10	0	0	0	0
1,000 (2)	ND	10	0	0	0	0

* Water accommodated fraction
§ND=not determined

LL50	>1000 mg/L at 96 hours.
NOEL	1000 mg/L.
Remarks – Results	All test fish appeared normal without any mortality during the test period. The TOC values were 2.9 mg/L in dilution water at the beginning of the test rather than < 2 mg/L.

CONCLUSION The analogue to the notified chemical is not considered to be harmful to fish up to the limit of its water solubility

TEST FACILITY EnviroSystems Division Resource Analysts, Inc. (1993a)

C.2.2. Acute toxicity to fish (Analogue)

TEST SUBSTANCE Analogue 6

METHOD	Modified OECD TG 203 Fish, Acute Toxicity Test – Semi-static.
Species	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	44 mg/L $CaCO_3$/L
Analytical Monitoring	Total organic carbon measurements
Remarks – Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for 4 hours before the solution was siphoned into the test chamber. 80-85 % of the media was renewed every 24 hours. The 1000 mg/L solutions was slightly cloudy at the start of each 24 hour period.

RESULTS

Concentration WAF mg/L*		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
0 (1)	ND§	10	0	0	0	0
0 (2)	ND	10	0	0	0	0
0 (3)	ND	10	0	0	0	0
1,000 (1)	ND	10	0	0	0	0
1,000 (2)	ND	10	0	0	0	0
1,000 (3)	ND	10	0	0	0	0

* Water accommodated fraction
§ND=not determined

LL50	>1000 mg/L at 96 hours.
NOEL	1000 mg/L.
Remarks – Results	All test fish appeared normal without any mortality during the test period.

CONCLUSION The analogue to the notified chemical is not considered to be harmful to fish up to the limit of its water solubility.

TEST FACILITY T.R. Wilbury Laboratories, Inc. (1998a)

C.2.3. Acute toxicity to aquatic invertebrates (Analogue)

TEST SUBSTANCE	Analogue 5
METHOD	Modified OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	176-180 mg $CaCO_3$/L
Analytical Monitoring	Total organic carbon measurements
Remarks - Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for one hour before the solution was siphoned into the test chamber. No insoluble material was observed.

RESULTS

Concentration WAF[*] mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control (1)	ND[§]	10	0	0
Control (2)	ND	10	0	0
100 (1)	ND	10	0	0
100 (2)	ND	10	0	0
300 (1)	ND	10	0	0
300 (2)	ND	10	0	0
1,000 (1)	ND	10	0	0
1,000 (2)	ND	10	0	0

[*] Water accommodated fraction
[§]ND=not determined

EL50	> 1000 mg/L at 48 hours
NOEL	1000 mg/L
Remarks - Results	All validity criteria for the test were satisfied. The TOC values were 2.9 mg/L in dilution water at the beginning of the test rather than < 2 mg/L. No immobilisation or abnormalities in behaviour or appearance were observed. The 48 h EL50 was determined to be > 1000 mg/L (WAF) based on nominal concentrations.
CONCLUSION	The analogue to the notified chemical is not considered to be harmful to aquatic invertebrates up to the limit of its water solubility.
TEST FACILITY	EnviroSystems Division Resource Analysts, Inc. (1993b)

C.2.4. Acute toxicity to aquatic invertebrates (Analogue)

TEST SUBSTANCE	Analogue 6
METHOD	Modified OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	164-168 mg $CaCO_3$/L
Analytical Monitoring	Total organic carbon measurements
Remarks - Method	All validity criteria for the test were satisfied.

The test solution was prepared as water accommodation fraction (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of the test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for four hours before the solution was siphoned into the test chamber. No insoluble material was observed.

RESULTS

Concentration WAF[*] mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control (1)	ND[§]	10	0	0
Control (2)	ND	10	0	0
Control (3)	ND	10	1	1
1,000 (1)	ND	10	1	1
1,000 (2)	ND	10	1	1
1,000 (3)	ND	10	0	0

[*] Water accommodated fraction
[§]ND=not determined

EL50	> 1000 mg/L at 48 hours
NOEL	1000 mg/L
Remarks - Results	All validity criteria for the test were satisfied. The 48 h EL50 was determined to be > 1000 mg/L (WAF) based on nominal concentrations.

CONCLUSION The analogue to the notified chemical is not considered to be harmful to aquatic invertebrates up to the limit of its water solubility.

TEST FACILITY T.R. Wilbury Laboratories, Inc. (1998b)

C.2.5. Algal growth inhibition test (Analogue)

TEST SUBSTANCE Analogue 5

METHOD Modified OECD TG 201 Alga, Growth Inhibition Test.

Species	*Selenastrum capricornutum*
Exposure Period	96 hours
Concentration Range	Nominal: 0, 125, 250, 500, 1000 and 1500 mg/L Actual: not determined
Auxiliary Solvent	None
Water Hardness	Not provided
Analytical Monitoring	Total organic carbon measurements
Remarks - Method	The test solution was prepared as water accommodation fraction (WAFs) due to low water solubility of the test substance. The WAFs were prepared by adding the weighed amount of the test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for approximately one hour before the solution was siphoned into the test chamber. No insoluble material was observed.

RESULTS

Number of cells		*Growth*	
EL50 mg/L at 96 h	*NOEL mg/L*	*EL50 mg/L at 96 h*	*NOEL mg/L*
1,100	125	>1,500	125

Remarks - Results	All validity criteria for the test were satisfied. The 96 h EL50 was determined to be > 1,500 mg/L based on growth rate. The corresponding NOEL was determined to be 125 mg/L.

CONCLUSION The analogue to the notified chemical is not considered to be harmful to

algae up to the limit of its water solubility.

TEST FACILITY T.R. Wilbury Laboratories, Inc. (1994)

C.2.6. Algal growth inhibition test (Analogue)

TEST SUBSTANCE Analogue 6

METHOD Modified OECD TG 201 Alga, Growth Inhibition Test.
Species *Selenastrum capricornutum*
Exposure Period 96 hours
Concentration Range Nominal: 0 and 1,000 mg/L
Actual: not determined
Auxiliary Solvent None
Water Hardness Not provided
Analytical Monitoring Total organic carbon measurements
Remarks - Method The test solution was prepared as water accommodation fraction (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of the test substance into water followed by stirring for 24 hours. The mixture was allowed to stand for approximately four hours before the solution was siphoned into the test chamber. No insoluble material was observed.

RESULTS

Number of cells		*Growth*	
EL50	*NOEL*	*EL50*	*NOEL*
mg/L at 96 h	*mg/L*	*mg/L at 96 h*	*mg/L*
>1,000	1000	>1,000	1000

Remarks - Results All validity criteria for the test were satisfied. The 96 h EL50 was determined to be > 1,000 mg/L based on growth rate. The corresponding NOEL was determined to be 1000 mg/L.

CONCLUSION The analogue to the notified chemical is not considered to be harmful to algae up to the limit of its water solubility.

TEST FACILITY T.R. Wilbury Laboratories, Inc. (1997)

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