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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Z-91

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (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 Ageing, 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, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also 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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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
LUBRIZOL INTERNATIONAL, INC
28 RIVER ST
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, CAS Number, Molecular Formula, Structural Formula, Molecular Weight, Means of Identification, Purity, Identity of Impurities, Details of Use, and Import Volumes.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: Dissociation constant, particle size, flammability limits, explosive properties, acute inhalation toxicity, induction of germ cell damage and bioaccumulation, use of analogue chemicals for physicochemical, toxicological, ecotoxicological studies and environmental fate studies.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Z-91

OTHER NAME(S)
OS224091

MOLECULAR WEIGHT
>500 Da,

ANALYTICAL DATA
Reference NMR, UV and IR spectra were provided.

3. COMPOSITION

DEGREE OF PURITY >90%

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

All physical and chemical properties were conducted on an analogue 1.

APPEARANCE: Clear tan liquid (notified chemical, temperature not specified)

Property	Value	Data Source/Justification
Melting Point/Freezing Point	38.85°C	Measured
Boiling Point	382°C at 101.3 kPa	Measured
Relative Density	0.963 at 20°C	Measured
Vapour Pressure	1.2 x 10^{-5} kPa at 25°C	Measured
Water Solubility	<2.60 x10^{-4} g/L at 20°C	Measured
Hydrolysis as a Function of pH	Half-life 15.8 days at pH 8, 158 days at pH 7	Estimated
Partition Coefficient (n-octanol/water)	log P_{ow} > 9.4 at 30°C	Analogue data
Adsorption/Desorption	log K_{oc} > 5.63 at 30°C	Analogue data
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Not determined	The notified chemical is a waxy liquid/low temperature melting liquid.
Flash Point	174°C at 102.22 kPa	Measured
Flammability	Not predicted to be highly flammable.	Estimated based on chemical structure and low vapour pressure.
Oxidising properties	Not predicted to be an oxidising agent.	Estimated based on chemical structure.
Autoignition Temperature	366 ± 5°C	Measured
Explosive Properties	Not predicted to be explosive.	Estimated based on chemical structure and oxygen balance.

DISCUSSION OF PROPERTIES
The notified chemical is expected to have very low water solubility and high partition coefficient, based on its structure. These expected properties are typical of engine oil fluids, and are supported by measured data for a closely related analogue. For full details of tests on physical and chemical properties, please refer to Appendix A.

Reactivity
There are no known hazardous decomposition products or incompatibility with other substances.

Dangerous Goods classification
Based on the available data, the notified chemical is not classified as a Dangerous Goods according to the Australian Dangerous Goods Code (NTC, 2007).

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 either as part of additive concentrate containing <20% of the notified chemical or as a finished engine oil additive containing <5% of the notified chemical.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	40-70	40-70	40-70	40-70	40-70

PORT OF ENTRY
Not stated

IDENTITY OF MANUFACTURER/RECIPIENTS
The notified chemical will not be manufactured in Australia. However, blending and packaging of engine oil containing the notified chemical will occur at different sites in Australia.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported either as part of a concentrate or as a finished engine oil additive in 20 tonnes isotainers or 205L steel drums. The drums would then be transported to the customers processing facility by truck or rail and storage would be in these containers.

USE
The notified chemical is intended for use as an engine oil additive at concentrations of <5%. Engine oils containing the notified chemical will be used in vehicle manufacturing, mechanical workshops and by members of the public for do-it-yourself (DIY) use.

OPERATION DESCRIPTION
The notified chemical will be imported either as part of a concentrate or as a finished engine oil additive. If formulation into engine oil additive is necessary, it will be performed by customers at their sites.

A typical formulation operation would involve blending the concentrate containing the notified chemical with oil and possibly other additives. The concentrate containing the notified chemical will be decanted from the drums to the tanks where it would be mixed with oil and possibly other additives. After blending, the engine oil which now contains the notified chemical at <5%, would be packaged into containers. Packages can range in size from 1L to 205L. Packaging equipment is expected to be automated and housed within or near the blending operation area. The blending facility is expected to be well ventilated and fully automated.

The finished engine oil containing the notified chemical will be supplied in bulk to automobile manufacturers for 'factory fill' applications. Additionally, it may also be supplied in smaller containers for use in service applications through garages or sold to the public for DIY use.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	2-3	1-3	4-6
Plant Operation	2-3	<1	50
Maintain/clean	2-3	2-4	10-20
Plant Operator-Sampling	1	<1	100
End user	1-3	2-4	Typically < 20

EXPOSURE DETAILS
Transport and storage
Transport and storage workers are not likely to be exposed to the notified chemical except in the case of an accident involving damage to the packaging.

Blending of engine oil products
The blending facility is expected to be well ventilated and fully automated. Therefore, exposure will mostly be limited to transfer operations in mixing vessels, residues in lines, and on coupling and occasionally from leaks and spills. Dermal contamination would be the main route of occupational exposure. Some inhalation exposure could occur if mists are generated during blending processes. Workers are expected to wear nitrile or neoprene gloves, chemical goggles or face shield, and long sleeve shirt. Where potential for contact with material exists, a chemical protective suit or apron is expected to be worn. A full face respirator with a combination of organic vapour and dust/mist cartridge will be used if the recommended exposure limit is exceeded.
Samples will be taken from blend vessels during the blending process. Dermal exposure may occur when a plant operator will open a valve and fill a small container. To minimise exposure, the plant operator is expected

to wear gloves, goggles and a long sleeved shirt as minimum persona protective equipment (PPE).

The packaging equipment is expected to be automated and housed within or near the blending operation area. An enclosed or open filling system may be used. Dermal contact would be the main route of occupational exposure and the packaging workers are expected to wear aprons, gloves and safety glasses to minimise exposure.

End use
Workers may be exposed to engine oils containing the notified chemical at less than 5% during use in vehicle manufacturing or mechanical workshops.

At car manufacturers, the finished engine oil will be added to engines using a dip-pipe and pump. This transfer is mechanical and exposure is unlikely. There is a potential for dermal exposure from drips, spills and splashes as well as from handling equipment contaminated with engine oil. Workers are expected to wear appropriate personal protective equipment such as long sleeve shirts and gloves to minimize dermal exposure. Ocular exposure will be minimal as goggles are worn when transferring engine oils. Overall exposure to the notified chemical will be low, given the low concentration (<5%) of the notified chemical in the finished engine oils.

At mechanical workshops, professional users such as mechanics may experience dermal or ocular exposure to the final product containing the notified chemical at <5%, when adding the engine oil to the automobile and other machinery. The risk of both dermal and ocular exposure may be reduced by wearing gloves, long sleeve shirts and goggles. Overall exposure to the notified chemical will be low, given the low concentration (<5%) of the notified chemical in the finished engine oils.

6.1.2. Public exposure
The end-use for the notified chemical will be as an engine oil additive. Therefore, once added to the crankcase, the general public will not be exposed to the notified chemical in the engine oil since the engine crankcase operates as a closed system.

DIY users may experience dermal and ocular exposure to final products containing <5% of the notified chemical when adding the products to automobiles and other machinery. Exposure would be minimised if users wear gloves, goggles and a long sleeved shirt. Overall, public exposure is expected to be limited due to its infrequent use and low concentration (<5%) of the notified chemical in finished engine oil.

6.2. Human health effects assessment

The results from toxicological investigations conducted on structurally related analogues are summarised in the table below. The analogue chemicals were found to be sufficiently similar to the notified chemical for toxicology assessment. The details of the toxicological investigations can be found in Appendix B.

Endpoint	*Test substance*	*Result and Assessment Conclusion*
Rat, acute oral toxicity	Analogue 1	LD50 > 2000 mg/kg bw low toxicity
Rat, acute dermal toxicity	Analogue 2	LD50 > 2000 mg/kg bw low toxicity
Rabbit, skin irritation	Analogue 2	slightly irritating
Rabbit, eye irritation	Analogue 2	severely irritating
Mouse, skin sensitisation – Local lymph node assay	Analogue 2	no evidence
Rat, repeat dose oral toxicity – 28 days.	Analogue 2	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	Analogue 1	non mutagenic
Genotoxicity – in vitro chromosome aberration	Analogue 2	non genotoxic

Toxicokinetics, metabolism and distribution.
Absorption through the skin is unlikely given the expected high log Pow (> 9.4). However, the high log Pow value and low molecular weight suggest absorption may occur through the gastrointestinal tract. The systemic effects observed in the repeat dose toxicity study on the analogue chemical indicate that absorption may occur via this route, although its extent is unknown.

Acute toxicity.
The notified chemical is likely to be of low acute oral and dermal toxicity. Toxicity via inhalation has not been tested.

Irritation and Sensitisation.
An analogue of the notified chemical was found to be severely irritating to the eyes based on a Rabbit Enucleated Eye Test (REET). The REET was performed in place of an *in vivo* acute eye irritation/corrosion test because the analogue chemical was suspected to be strongly irritating and/or corrosive. Treatment of enucleated rabbit eyes with the analogue chemical for 10 secs yielded the following effects: corneal opacity, sloughing, corneal swelling and fluorescein uptake. Based on these effects, the analogue chemical was considered to have the potential to cause severe ocular irritation and therefore an *in vivo* study was not performed due to animal welfare concerns. The notified chemical, based on its similarity to the analogue, is expected to be severely irritating to the eye.

An analogue of the notified chemical was found to be slightly irritating to the skin. The analogue at pH 1, indicated the potential for severe irritation or corrosion. Therefore, as a pre-screening test, the Transcutaneous Electrical Resistance (TER) Assay was performed. After treatment with the analogue chemical, the electrical conductivity across rat skin did not increase significantly indicating that it was unlikely to be corrosive. Further tests were conducted *in vivo* in rabbits, with a single application of the analogue chemical applied using a semi-occluded dressing. No adverse reactions were observed upon application of the analogue chemical for 3 minutes and 1 hour. However, after application for 4 hrs, well-defined erythema was observed in two animals persisting in one to 48 hrs. Very slight oedema was observed in two animals persisting in one to 48 hrs. Slight desquamation was also observed in two animals, 7 days after treatment. Therefore, the analogue of the notified chemical is considered to be slightly irritating to skin, but these effects were not sufficient for the analogue to be classified according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC: 1008 (2004)]. Based on its similarity to the analogue, the notified chemical can be expected to be slightly irritating to skin.

The notified chemical is not expected to be sensitising, as there was no evidence of skin sensitisation in a mouse local lymph node assay (LLNA) on an analogue of the notified chemical at concentrations up to 25%.

Repeated Dose Toxicity.
In the 28-day repeat dose oral toxicity study on an analogue of the notified chemical, increased liver weights and centrilobular hepatocyte enlargement were observed in males and females treated with 1000 mg/kg bw/day. As no necrotic or inflammatory changes were observed, these effects were considered to be adaptive changes.

Treatment-related increases in kidney weights were observed in males treated with 1000 mg/kg bw/day ($p<0.05$). Globular eosinophilic depositions were found in the tubular epithelium of males dosed at 150 and 1000 mg/kg bw/day. These effects were considered to be male-rat specific changes, typical of a hydrocarbon nephropathy that does not occur in female rats and other species. These effects were not considered to be relevant to human health evaluation.

The No Observed Adverse Effect Level (NOAEL) for the notified chemical is expected to be 1000 mg/kg bw/day, based on the absence of adverse effects at this dose level in a study on the analogue chemical.

Mutagenicity.
Analogue 1 was found to be non-mutagenic in a bacterial reverse mutation test. Analogue 2 showed no evidence of clastogenicity to human lymphocytes *in vitro*, either with or without metabolic activation. Based on these results, the notified chemical is not expected to be a mutagen.

Health hazard classification
The REET was conducted according to Good Laboratory Practices (GLP) for the analogue chemical and based on the results of the analogue chemical, the notified chemical can be reasonably expected to produce severe eye irritation *in vivo*. In its most recent *Manual of Decisions*, the European Chemicals Bureau (ECB) states that a positive result in the REET is sufficient for classification with *R41 Risk of serious damage to eyes* (ECB, 2006).

Therefore, the notified chemical should be classified as:

R41 - Risk of serious damage to eyes

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Based on the available data, the notified chemical may cause severe eye damage and therefore scenarios involving ocular exposure are of greatest concern. The concentration cut-off levels for mixtures containing severe eye irritants are ≥10% for classification as R41 and ≥ 5% to < 10% for classification as R36 (NOHSC, 2004). These cut-off levels would apply to the notified chemical imported as additive concentrate (<20%) but not to the finished engine oil product (<5%).

Transport and warehouse workers and plant operators involved in blending of the concentrate product would be at risk of eye damage, if ocular exposure to the notified chemical occurred during handling of the imported additive concentrate (<20%). Maintenance workers and plant operators would also be at risk of eye damage if ocular exposure to the notified chemical (<20%) occurred during cleaning of blending equipment or during handling of the concentrate additive prior to blending into the final product.

Workers involved in handling of the finished product during blending and packaging may also be at risk of eye irritation. However, the risk posed to these workers is considered to be lower given the lower concentration of the notified chemical in these products (< 5%). The risk is further reduced by the use of automatic equipments and PPE (long sleeve shirt or aprons, gloves and goggles or safety glasses).

The risk of eye irritation would be minimal during the end-use applications as notified chemical would be present at a lower concentration (<5%). The risk will be further reduced by the use of mechanical equipment and PPE.

In all worker activities, the risk of eye damage or irritation would be minimised by the use of recommended eye/face protection at all times.

Given the low severity of observed effects in the rabbit test, and given the anticipated use of gloves and a long sleeved shirt to minimise exposure to the skin, the risk of skin irritation to dermally exposed workers is not considered to be unacceptable.

6.3.2. Public health

The risk to the public is not considered unacceptable assuming that most consumers are not DIY users. For DIY users changing engine oil containing the notified chemical, there is a risk of adverse eye effects resulting from ocular exposure during the draining of used engine oil. However, the risk is not considered unacceptable, given that draining of engine oil is an infrequent event and the concentration of the notified chemical in the engine oil is < 5%.

There is also potential for dermal exposure in DIY users from splashes, drips and spills of engine oils containing the notified chemical. The risk is not considered to be unacceptable given the limited adverse effects observed in the skin irritation study, the infrequent handling of engine oil containing the notified chemical and the low concentration of the notified chemical in engine oil products (< 5%).

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

At the blending facilities, release during the highly automated blending process is not expected. The equipment used will typically be cleaned with oil, with these washings used in the formulation of the next batch or another oil blend. In these situations release would occur through accidental spills, which would be recycled or collected for thermal decomposition. Any of the notified chemical remaining in the import containers, expected to be < 1% of the contents, would be washed out and recycled or collected for incineration.

RELEASE OF CHEMICAL FROM USE
Some minor, diffuse exposure will result from spills during addition to and removal of oil from vehicles. Around 86% of oil changes take place in specialised automotive service centres, where release of the notified chemical from professional activities should be disposed of appropriately. The remaining 14% will be removed by DIY enthusiasts. The DIY proportion of oil changes could potentially lead to improper disposal of used oil (55%) to soils or sediments and storm water drains.

RELEASE OF CHEMICAL FROM DISPOSAL
Iso-containers and drums should be sent for cleaning and reconditioning by a licensed company. The resultant washings from such companies are typically passed to an on site waste treatment facility and any waste sludge is typically disposed of by thermal decomposition.

Used oil, drained from crankcases at specialised automotive service centres, is expected to be disposed of either to oil recycling centres or thermal decomposition.

Only around 20% of used oil removed by DIY enthusiasts is collected for recycling. Approximately 25% is buried or disposed of in landfill, 5% is disposed of into storm water drains and the remaining 50% is used in treating fence posts, killing grass and weeds or disposed of in other ways.

7.1.2 Environmental fate

The notified chemical is likely to mainly be disposed of by thermal decomposition to recover calorific value. Smaller amounts may be consigned to landfill, or disposed of inappropriately to land or stormwater. Thermal decomposition would destroy the notified chemical, while disposal to land or landfill would result in its immobilisation because of the strong sorption to soil organic carbon. If disposed of to water, the notified chemical is likely to spread across the surface of the water and sorb to suspended solids and sediment. The notified chemical is not expected to be readily biodegradable, based on data for a closely related analogue (analogue 1), but can be expected to degrade in the environment as the analogue underwent substantial biodegradation in a carbon dioxide evolution test. While there was some indication of uptake by fish in toxicity testing with an analogue chemical, bioaccumulation is not expected to be a significant pathway because the notified chemical has a very low water solubility and high octanol-water partition coefficient ($> 10^7$) and is therefore not expected to be bioavailable to aquatic organisms.

For the details of the environmental fate studies, refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

A worst case PEC might be calculated if it is assumed that 0.7% of the notified chemical (maximum 490 kg) is released 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 490 kg and the annual volume of water drained from this region estimated to be approximately 250 x 10^6 m^3, the resultant PEC is approximately 2.0 µg/L. It should be stressed that this result reflects a worst case scenario, as in reality releases of the notified chemical would be more diffuse and at lower levels.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on analogues of the notified chemical are summarised in the table below. The analogue for fish, algal and bacterial testing is closely related in structure to the notified chemical, but has a lower molecular weight. It was notified as analogue 2 by the same notifier. The analogue for the daphnid test was notified as analogue 1. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96-hr LC50 > 0.78 mg/L	Not toxic to *Onchorhynchus mykiss* up to the limit of water solubility.
Daphnia Toxicity	48-hr EC50 > 1 mg/L	Not toxic to *Daphnia magna* up to the limit of water solubility.
Algal Toxicity	E_rC50 > 0.55 mg/L	Not toxic to algae up to the limit of water solubility.
Inhibition of Bacterial Respiration	IC50 > 1000 mg/L	Not considered harmful to bacterial respiration.

Testing of the analogue chemicals was complicated by their very low solubility and the difficulty of maintaining them in aqueous solution. Median effect concentrations in acute testing were consistently above the limit of water solubility. Similar difficulties and outcomes would be expected from testing of the notified chemical.

7.2.1 Predicted No-Effect Concentration

An upper limit to the PNEC can be calculated by application of a hundred-fold assessment factor to the EC50 of 0.55 mg/L (lower limit) in algae.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
E_rC50 (algae)	> 0.55	mg/L
Assessment Factor	100	
PNEC:	> 5.5	µg/L

7.3. Environmental risk assessment

The risk quotients (Q = PEC/PNEC) are tabulated below.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	2.0	> 5.5	**< 0.36**
Q - Ocean	0.2	> 5.5	**< 0.04**

Based on the data from an acceptable analogue of the notified chemical, the calculated risk quotients remain below unity, indicating a low risk to aquatic life even under the conservative exposure assumptions outlined above. The PEC overestimates the likely level of exposure, as it reflects a worst case scenario with no consideration of the strong hydrophobicity of the notified chemical, which would favour sorption to sediment rather than dissolution in the water column.

Accidental spills of the notified chemical to water can be expected to be harmful to aquatic life, as it would be likely to coat biological membranes in such situations, but the notified chemical is not expected to pose a risk to the environment when it is used as proposed in engine oils.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

A REET was performed on an analogue of the notified chemical (analogue 2), in place of an *in vivo* acute eye irritation/corrosion test because the analogue chemical was suspected to be strongly irritating and/or corrosive.

The REET is conducted according to Good Laboratory Practices (GLP) and the test results can be reasonably expected to produce severe eye irritation *in vivo*. In addition, the European Chemicals Bureau (ECB) believes that a positive result in the REET is sufficient for classification with R41: Risk of serious damage to eyes (ECB, 2006). Therefore, the notified chemical should be classified as:

R41 - Risk of serious damage to eyes

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations, 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Human Health	Category 1	Danger: Causes serious eye damage

For environmental purpose, the classification of the notified chemical using GHS) (United Nations 2003) is inapplicable. The analogue chemical used as the basis for this determination showed no acute toxicity to aquatic organisms up to the limit of water solubility, and exhibits the potential for rapid biodegradation.

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

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio, the very low water solubility and the reported use pattern, the notified chemical is not considered to pose a risk to the environment

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:
  - *R41: May cause serious eye damage*

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - *≥10%: R41 May cause serious damage to eyes*
  - *5%≤ conc ≤10%: R36 Irritating to eyes*

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices:
  - *Eyewash stations should be maintained at all sites where the notified chemical (as introduced and in the blending concentrate) is handled.*

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced (<20%) and in the blending concentrate (< 20%):
  - *Eye/face protection.*

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]

workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by 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(2) of the Act; if
- the function or use of the chemical has changed from engine oil additive, or is likely to change significantly;
- the amount of chemical being introduced has increased from 70 tonnes per annum, 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.

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

All physical and chemical properties were conducted on analogue 1.

Melting Point/Freezing Point 38.85 ± 0.5°C at 102.22 kPa

Method	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	The DSC method was employed
Test Facility	SafePharm Laboratories Ltd. (2007a)

Boiling Point 382°C at 101.3 kPa

Method	OECD TG 103 Boiling Point. EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	The DSC method was employed. The notified chemical bubbled from 220°C and changed to a light brown colour from about 280°C. This observation is possibly indicative of decomposition.
Test Facility	SafePharm Laboratories Ltd. (2007a)

Relative Density 0.963 at 20 ± 0.5°C

Method	OECD TG 109 Density of Liquids and Solids. EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Determined using the pycnometer method.
Test Facility	SafePharm Laboratories Ltd. (2007a)

Vapour Pressure 1.2×10^{-5} kPa at 25°C

Method	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Determined with a vapour pressure balance between 23-33°C.
Test Facility	SafePharm Laboratories Ltd. (2007b)

Water Solubility $< 2.60 \times 10^{-4}$ g/L at 20°C

Method	OECD TG 105 Water Solubility. EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Determined using the Flask Method. HPLC used for concentration analysis. No peaks of test material were detected in definitive tests with HPLC, indicating very low water solubility of the test chemical. Using chemical estimation software WSKOWWIN, version 1.41, © 2000 US Environmental Protection Agency, the test material has a predicted water solubility of 4.197×10^{-6} mg/L.
Test Facility	SafePharm Laboratories Ltd. (2007a)

Hydrolysis as a Function of pH Half-lives of 15.8 days at pH 8 and 158 days at pH 7

Method	Estimated using HYDROWIN version 1.67, © 2000 US Environmental Protection Agency.
Remarks	A hydrolysis test could not be conducted according to OECD TG 111 due to the very low water solubility of the notified chemical. Hydrolysis of an analogue of the notified chemical was therefore estimated using Episuite computer-based estimation software, indicating hydrolysis could be an important factor under alkaline conditions.
Test Facility	SafePharm Laboratories Ltd (2007a)

Partition Coefficient (n-octanol/water) log P_{ow} > 9.4

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks The test was conducted with an analogue of the notified chemical, using the HPLC Method. The dead time was determined by using Thiourea. The column temperature was set as 30ºC. The partition coefficient has been established as log P_{ow} > 9.40 because the retention time was longer than that of 1-pentyltridecane. High P_{ow} is expected according to the low water solubility of the notified chemical and its analogue
Test Facility SafePharm Laboratories Ltd (2007a)

Adsorption/Desorption – screening test log K_{oc} > 5.63

Method OECD TG 121 Estimation of the Adsorption Coefficient (K_{oc}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks The test was conducted with an analogue of the notified chemical, using the HPLC screening method. The dead time was determined by using formamide. Column temperature was set as 30˚C. Testing was carried out at neutral pH due to the absence of any possible dissociating functional groups in the notified chemical. The retention time of the notified chemical was longer than DDT. High K_{oc} is expected from the high P_{ow} and the low water solubility of the notified chemical and its analogue.
Test Facility SafePharm Laboratories Ltd (2007a)

Flash Point 174 ± 2ºC at 102.22 kPa

Method EC Directive 92/69/EEC A.9 Flash Point.
Remarks Closed cup method.
Test Facility SafePharm Laboratories Ltd. (2007b)

Autoignition Temperature 366 ± 5ºC

Method EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility SafePharm Laboratories Ltd. (2007b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

All toxicology studies were conducted on analogues 1 & 2.

B.1. Acute toxicity – oral

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method
Species/Strain	Rat/Sprague-Dawley
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations

RESULTS

LD50	>2000 mg/kg bw
Signs of Toxicity	There were no signs of systemic toxicity.
Effects in Organs	There were no remarkable necropsy findings.
Remarks - Results	None
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	SafePharm (2007c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Sprague-Dawley
Vehicle	Test substance administered as supplied.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	None
Signs of Toxicity - Systemic	There were no treatment related clinical signs observed.
Effects in Organs	There were no treatment related effects observed in organs.
Remarks - Results	None
CONCLUSION	The notified chemical, based on its similarity to the analogue, may be expected to be of low toxicity via the dermal route.
TEST FACILITY	Safepharm (2006a)

B.3. Irritation – skin

TEST SUBSTANCE	Analogue 2
METHOD	
Species/Strain	Rabbit/New Zealand White

Number of Animals	3 (1 M, 2 F)
Vehicle	Test substance administered as supplied
Observation Period	7 days
Type of Dressing	Semi-occlusive.
Remarks - Method	The notified chemical was thought to be corrosive at a pH 1. Therefore before testing *in vivo,* a pre-test (Transcutaneous Electrical Resistance Assay) was conducted on rat skin. This predicted the notified chemical was not corrosive. A stepwise procedure involving 3-min and 1-hr semi-occluded applications of the notified chemical to one rabbit did not produce corrosive effects. Upon seeing no corrosive results after the 1-hr application, a main study involving a 4-hr application was conducted. The three rabbits (1 M, 2 F) used in the main study originated from two different suppliers. This was not considered to have a significant effect on the outcome of the study.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.33	1.67	1.33	2	72 hrs	0 D
Oedema	0	0.67	0.33	1	48 hrs	0

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

Remarks - Results	After semi-occluded application for 4 hrs, very slight erythema was observed in the male at 24 hrs but was not observed at 48 hrs. Well-defined erythema was observed in the two female rabbits at 24 hrs and persisted in one to 48 hrs. Very slight oedema was observed in two female rabbits at 24 hrs and persisted in one to 48 hrs. 7 days after treatment with the notified chemical, slight desquamation was observed in the two female animals.
CONCLUSION	The notified chemical, based on its similarity to the analogue, may be expected to be slightly irritating to the skin.
TEST FACILITY	Safepharm (2006b)

B.4. Irritation – eye

TEST SUBSTANCE	Analogue 2
METHOD	Rabbit Enucleation Eye Test (REET), conducted according to GLP. The Rabbit Enucleation Eye Test was conducted in place of the OECD TG 405 Acute Eye Irritation/Corrosion test.
Species/Strain	Rabbit
Number of Animals	3
Observation Period	240 minutes
Remarks - Method	Five enucleated rabbit eyes were excised and allowed to equilibrate for 30 mins in a Perspex clamp placed within a superfusion chamber. Saline solution was allowed to irrigate the surface of the cornea via a saline drip in the rear of the chamber. The eyes were re-examined after 30 mins of equilibration to ensure that no signs of irritation resulted from the excision. Corneal thickness was measured using an ultrasonic pachymeter. Any eyes with corneal swelling greater than 10% of the pre-enucleation measurement or stained with fluorescein were discarded. After inspection proceeding equilibration, three eyes held by Perspex

clamps were removed from the superfusion chamber and placed horizontally into a petri dish. 0.1 ml of the notified chemical (undiluted) was applied evenly to the surface of the cornea of three eyes. After ten seconds the notified chemical was washed off using a minimum 20 ml of saline solution. After treatment, the eyes were returned to the superfusion chamber as per pre-treatment. The remaining two eyes remained untreated and served as controls.

The thickness of the cornea was measured using an ultrasonic pachymeter pre-enucleation, post-equilibration and 60, 120, 180 and 240 mins following treatment. For each enucleated eye a measurement was made at the optical centre, and at four other locations at the apex of the cornea. A mean value for corneal thickness was calculated based on these four measurements. The corneal thickness for each eye at 60, 120, 180 and 240 mins following treatment was used to calculate the percentage change compared with the corneal thickness pre-treatment.

Corneal cloudiness was assessed pre-enucleation, post-equilibration and at approximately 60, 120, 180 and 240 mins following treatment. Examination of the eye was assessed using a slit-lamp biomicroscope.

The uptake of fluorescein by the corneal epithelium was assessed pre-enucleation, post-equilibration and approximately 240 mins following treatment using a cobalt blue filter of the split-lamp biomicroscope after application of Fluorescein Sodium drops.

RESULTS

Corneal cloudiness was observed in all test eyes during the study. Cloudiness persisted at the same level at all observation periods.
Sloughing was observed in all test eyes from 120 mins to 240 mins following treatment.
Fluorescein uptake was observed in all test eyes at 240 mins following treatment.
Corneal swelling was observed in all test eyes with a maximum value of 113.9% of the thickness of the cornea post-equilibration.

Remarks - Results: The results of the REET indicated the potential for severe eye irritation. Accordingly, the *in vivo* eye irritation test was considered unnecessary and was not performed in the interests of animal welfare.

CONCLUSION: The notified chemical, based on its similarity to the analogue, may be expected to be severely irritating to the eye.

TEST FACILITY: Safepharm (2006c)

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

TEST SUBSTANCE: Analogue 2 in acetone/olive oil (4:1)

METHOD: OECD TG 429 Skin sensitisation: Local Lymph Node Assay.
- Species/Strain: Mouse/CBA/Ca CruBR
- Vehicle: Acetone/olive oil (4:1)
- Remarks - Method: No significant protocol deviations.
  Test concentrations were chosen on the basis of a preliminary screening test. A-Hexylcinnamaldehyde (Tech. 85%) was used as a positive control to test the sensitivity of the strain of mouse.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	2241.76	
5	2236.38	1.00
10	2872.57	1.28
25	5919.70	2.64
Positive Control		
5		3.53
10		5.39
25		8.23

Remarks - Results: No signs of systemic toxicity were noted.
At all concentrations the mean DPM was not significantly different ($p \geq 0.05$) to the vehicle control group. A stimulation index of <3 was recorded for all concentrations tested.

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the analogue chemical. Therefore, the notified chemical, based on its similarity to the analogue, is not expected to be sensitising.

TEST FACILITY: Safepharm (2006d)

B.6. Repeat dose toxicity

TEST SUBSTANCE: Analogue 2

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

Species/Strain: Rat/Sprague-Dawley Crl:CD (SD) IGS BR
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: None
Vehicle: Polyethylene glycol 400
Remarks - Method: No significant protocol deviations.
Dosages were determined by a preliminary 14-day range finding study, in which no mortality or serious toxicity were observed up to 1000 mg/kg bw/day. No urinalysis was performed.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	15	0
mid dose	5 per sex	150	0
high dose	5 per sex	1000	0

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

Clinical Observations
An increase in salivation was observed up to 10 mins after dosing in all animals dosed at 1000 mg/kg/day and occasionally persisted for up to 1 hour. Occasional staining around the eyes, mouth and fur were also observed at this dose level.

Salivation was also observed in males treated with 150 mg/kg/day up to 10 mins after dosing.

No other significant, treatment-related clinical signs were observed.

Laboratory Findings – Clinical Chemistry, Haematology
There were no treatment-related changes in the haematological parameters assessed.
Females treated at all dose levels showed a statistically significant increase in mean cell haemoglobin ($p<0.05$). However, the significance was minimal in each case ($p<0.05$) and was considered one lower than the expected control value and therefore the increases were considered unrelated to treatment.

Effects in Organs
All animals dosed at 1000 mg/kg bw/day showed increases in liver weights and males in that group also showed increases in kidney weight ($p<0.05$). No treatment-related effects were detected in animals treated in the mid and low dose groups. No macroscopic abnormalities were observed at necropsy.

Histopathology
Centrilobular hepatocyte enlargement was observed in all animals dosed at 1000 mg/kg/day.
Globular accumulations of eosinophilic material were observed in the tubular epithelium of three males dosed at 1000 mg/kg/day and in three males dosed at 150 mg/kg/day.

Remarks – Results
The centrilobular hepatocyte enlargement and increased liver and kidney weights observed in animals dose at 1000 mg/kg bw/day may be considered to be adaptive metabolic responses to treatment with a xenobiotic. The eosinophilic globular accumulations observed in three males at 1000 and 150 mg/kg bw/day were considered to be characteristic of a typical hydrocarbon nephropathy peculiar to the male rat and absent in female rats and other species. Therefore these effects would not be considered relevant to human health.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) for the analogue chemical was established as 1000 mg/kg bw/day in this study, based on the absence of any treatment-related adverse health effects.

The No Observed Effect Level (NOEL) for the analogue chemical considered to be 150 mg/kg bw/day for females and 15 mg/kg bw/day for males.

The notified chemical, based on its similarity to the analogue, is expected to have a NOAEL of 1000 mg/kg bw/day.

TEST FACILITY Safepharm (2007d)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 471 Bacterial Reverse Mutation Test.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction 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	Acetone
Remarks - Method	No significant protocol deviations. Plate incorporation method.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5000			
Test 1		> 5000	≥ 1500	Negative
Test 2		> 5000	≥ 1500	Negative
Present	> 5000			
Test 1		> 5000	≥ 1500	Negative
Test 2		> 5000	≥ 1500	Negative

Remarks - Results

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

TEST FACILITY Safepharm (2007e)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Analogue 2

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain Human
Cell Type/Cell Line Lymphocyte
Metabolic Activation System S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver.
Vehicle DMSO
Remarks - Method No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 14.61, 29.22*, 58.44*, 87.66*, 116.88, 175.32	4 hrs	20 hrs
Test 2	0*, 7.31, 14.61*, 29.22*, 58.44*, 87.66, 116.88	24 hrs	24 hrs
Present			
Test 1	0*, 58.44, 116.88, 233.75*, 350.63*, 467.5*, 701.25	4 hrs	20 hrs
Test 2	0*, 14.61, 29.22*, 58.44*, 116.88*, 233.75, 467.5	4 hrs	20 hrs

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>58.44	>87.66	29.22	Negative
Test 2	>58.44	>58.44	233.75	Negative
Present				
Test 1	>233.75	>467.5	58.44	Negative
Test 2		>116.88	58.44	Negative

Remarks - Results In Test 2 with metabolic activation the notified chemical induced small increases in the number of cells with chromosome aberrations. The increases were not considered dose-related. No statistically significant increases in aberrations were noted in the other three test groups.
The notified chemical did not induce a statistically significant increase in the numbers of polyploid cells at any dose level in either of the exposure groups.

	All vehicle (solvent) controls had frequencies of cells with aberrations within the range expected for normal human lymphocytes. All the positive control materials induced statistically significant increases in the frequency of cells with aberrations, indicating the satisfactory performance of the test and of the activity of the metabolising system.
CONCLUSION	The analogue chemical was not clastogenic to human lymphocytes cell treated *in vitro* under the conditions of the test. Therefore, the notified chemical, based on its similarity to the analogue, is expected to be non-genotoxic.
TEST FACILITY	Safepharm (2007f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Analogue 1

METHOD
- Inoculum: Activated Sewage Sludge Micro-organisms
- Exposure Period: 28 days
- Auxiliary Solvent: None
- Analytical Monitoring: DOC was detected using a Shimadzu TOC-5050A TOC analyser.
- Remarks - Method: Activated sewage sludge was exposed to 14.4 mg/L (10 mg carbon/L) of the test material for 28 days at 21˚C in darkness for ready biodegradability test.

The degradation of the test material was assessed by the determination of carbon dioxide produced. Control test with inoculum, standard test with standard material sodium benzoate, and toxicity control test were conducted for validation purposes.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	33	6	41
14	46	14	65
22	61	22	97
28	78	28	100

Remarks - Results: The total CO_2 evolution in control test on Day 28 was 27.82 mg/L, within the limitation of 40 mg/L; the IC/TC ratio of the test material suspension in the mineral medium at the start of the test was 0, within the limitation of 5%; the difference between the values for CO_2 production at the end of the test for the replicate test vessels was < 20%. All validation criteria given in OECD Test Guideline were satisfied and the study is considered valid.

Sodium benzoate attained 100% degradation after 28 days thereby confirming the suitability of the inoculum and test conditions.

Analogue 1 attained 78% degradation after 28 days and failed to satisfy the 10-day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation exceeding 10%. The test material cannot therefore be considered to be readily biodegradable under the strict terms and conditions of the Test Guideline. However, the analogue 1 has exhibited the potential for rapid biodegradation.

CONCLUSION: The notified chemical, based on its similarity to the analogue 1, cannot be considered to be readily biodegradable; however, it exhibits the potential for rapid biodegradation.

TEST FACILITY: SafePharm Laboratories Ltd (2007g)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 203 Fish, Acute Toxicity Test -in juvenile rainbow trout (*Onchorhynchus mykiss*) with exposure period of 96 hours. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - in juvenile rainbow trout (*Onchorhynchus mykiss*) with exposure period of 96 hours.
Species	juvenile rainbow trout (*Onchorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L (pH 8)
Analytical Monitoring	GC/MS was used for determination of the concentration of the notified chemical.
Remarks – Method	Two separate pilot tests were realized with rainbow trout (10 for each test) at the saturated concentration 1.5 mg/L of the notified chemical. A semi-static test regime was employed in the test involving a daily renewal of the test medium. A marked decline in concentration of the notified chemical was noted during the toxicity test, which was considered predominantly the result of absorption by fish rather than hydrolysis in the water column as the decline in test vessels was far greater than observed during stability analyses.

Results

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
1.5	0.78*	10	0	0	0	0	0

* Time-weighted mean test concentration calculated considering the decline of concentration during the test.

LC50	> 0.78 mg/L at 96 hours.
NOEC	0.78 mg/L at 96 hours.
Remarks – Results	The decline in concentration may indicate uptake of the test material by fish. No sub-lethal effects were observed at 1.5 mg/L, the solubility of the analogue chemical in water. The test result from the analogue is considered applicable to the notified chemical.
Conclusion	The analogue is not considered to be toxic to *Onchorhynchus mykiss* up to the level of its water solubility. Therefore, the notified chemical, based on its similarity to the analogue, is not expected to be toxic to fish.
Test Facility	SafePharm Laboratories Ltd (2007h)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – 48h static
Species	*Daphnia magna*

Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC/MS using an external standard was used to monitor concentration in test samples.
Remarks - Method	Tests were conducted at a range of nominal loading rates of 10, 18, 32, 56 and 100 mg/L of the analogue chemical at 21-22˚C under static test conditions. Due to the low water solubility and complex nature of the test material, test medium was prepared as a Water Accommodated Fraction (WAF). To prepare the WAFs of different loading rates, amounts of notified chemical (25, 45, 140 and 250 mg) were each separately added to the surface of 2.5 L of reconstituted water to give the 10, 18, 32, 56 and 100 mg/L loading rates respectively. After the addition of the analogue chemical, the reconstituted water was stirred by magnetic stirrer using a stirring rate such that a vortex was formed to give a dimple at the water surface (slow-stir method). After 47 hours of stirring the mixtures were allowed to stand for 1 hour. A wide bore glass tube, covered at one end with Nescofilm was submerged into the vessel, sealed end down, to a depth of approximately 5 cm from the bottom of the vessel. A length of Tygon tubing was inserted into the glass tube and pushed through the Nescofilm seal. The aqueous phase or WAFs were removed by mid-depth siphoning (the first 75-100 mL discarded) to give the 10, 18, 32, 56 and 100 mg/L loading rate WAFs. Microscopic inspection of the WAF showed no micro-dispersions or undissolved test material to be present. Analysis of the test preparations at 0 hours gave results of < LOQ. A positive control was conducted using potassium dichromate as the reference material at concentrations of 0.32, 0.56, 1.0, 1.8 and 3.2 mg/L under static test conditions. The mean 48-Hour EC50 calculated from all positive controls was 0.81 mg/L (sd = 0.21).

RESULTS

Nominal Concentration mg/L (WAF)		*Number of D. magna*	*Number Immobilised*	
			24 h	*48 h*
10	-	20*	0	0
18	-	20	0	0
32	-	20	0	0
56	-	20	0	5
100	-	20	0	13

*Replicate tests were carried out with 10 daphnids in each.

LC50	82 mg/L (WAF) at 48 hours
NOEC	32 mg/L (WAF) at 48 hours
Remarks - Results	No immobilization observed up to loading rate of 32 mg/L WAF. Analysis of samples taken at 0-hours showed measured concentration was below the limit of quantitation (LOQ) of the analytical method which was assessed to be 0.0047 mg/L. Those results indicate that the test medium might actually have a loading of up to the limit of the water solubility. In this scenario the toxicity result could only be referred to the solubility limit of the analogue chemical.
CONCLUSION	The analogue is not considered to be toxic to *Daphnia magna* up to the level of its water solubility. Therefore, the notified chemical, based on its similarity to the analogue, is not expected to be toxic to daphnids.
TEST FACILITY	SafePharm Laboratories Ltd (2007i)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 201 Algae, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0.84 mg/L Actual: 0.361-0.84 mg/L
Auxiliary Solvent	None
Water Hardness	15 mg $CaCO_3$/L
Analytical Monitoring	GC/MS for analysis of the test substance concentration.
Remarks - Method	*Desmodesmus subspicatus* with density of 4×10^3 cells per ml was exposed for 72 hours to the test material of an initial concentration of 0.84 mg/L at pH 7.2 at beginning and 7.7 at the end of the test. The test solution was a saturation solution of 0.84 mg/L analogue chemical. The test was taken in six replicates.

RESULTS

Biomass		*Growth*	
E_bC_{50} *mg/L at 72 h*	NOE_bC *mg/L*	E_rC_{50} *mg/L at 72 h*	NOE_rC *mg/L*
> 0.55	0.55	> 0.55	0.55

Remarks - Results

The cell concentration of the control cultures increased by a factor of 45 after 72 hours, which was in line with the OECD Guideline that states the enhancement must be at least by a factor of 16 after 72 hours.

The mean variation coefficient for the control section-section daily growth rates was 61% and hence exceeded the recommended maximum of 35% given in the OECD Guideline. This was considered as the result of the abnormally high concentration of the algal suspension added to the test medium. Given that the validation criteria relating to increase in control cell density and coefficient of variation of the control average growth rates for the test period were satisfied the study is considered valid.

A marked decline in the concentration of the analogue chemical in the test period was detected and was considered the result of hydrolysis and adsorption of the analogue chemical to the organism during the test. Geometric mean measured concentrations of the samples were thus calculated and used for toxicity characterization of the analogue chemical to algae in water.

No statistically significant inhibition to alga in terms of growth rate, yield or biomass integral was observed up to the limit of its water solubility.

CONCLUSION	The notified chemical, based on its similarity to the analogue, is not expected to be toxic to algae.
TEST FACILITY	SafePharm Laboratories Ltd (2007j)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated Sewage Sludge
Exposure Period	3 hours
Concentration Range	Nominal: 1000 mg/L Actual: 1000 mg/L
Remarks – Method	Three replicate tests were conducted by exposing activated sewage sludge to 1000 mg/L dispersion of the analogue chemical. The test water had a total hardness of 100 mg/L as $CaCO_3$. Variation in respiration rates of control tests was 3% after both 30 minutes and 3 hours contact. EC_{50} (3- hour contact time) for reference substance 3,5-dichlorophenol was 5.4-9.0 mg/L. The study is thus considered valid according to Test Guideline.
RESULTS	No significant effect was observed at the dispersion of analogue chemical at concentration of 1000 mg/L highly in excess of the solubility of the chemical.
IC50	> 1000 mg/L
NOEC	1000 mg/L
Remarks – Results	
CONCLUSION	The notified chemical, based on its similarity to the analogue, is not expected to be harmful to microbial respiration.
TEST FACILITY	SafePharm Laboratories Ltd (2007k)

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