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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Component 3 (Mixed sulfonic acid, calcium salts)

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Oronite Australia Pty Ltd (ABN: 16 101 548 716)
Level 8, 520 Collins St
Melbourne, Victoria, 3000

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Chemical name
CAS number
Molecular formula
Structural formula
Molecular weight
Spectral data
Purity
Identity of toxic impurities
Non-hazardous impurities
Identity and percentage of additives
Manufacture or import volumes
Identity of manufacturing sites
Concentration of notified chemical in product

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:

Melting point/ Boiling point
Density
Vapour pressure
Water solubility
Hydrolysis as a function of pH
Partition co-efficient
Absorption/desorption
Dissociation constant
Flammability limits
Autoignition temperature
Acute oral toxicity
Acute dermal toxicity
Acute inhalation toxicity
Skin irritation
Eye irritation
Skin sensitisation
28-day repeat dose toxicity
90 day repeat dose toxicity
Induction to point mutations
Chromosome damage
Fish acute toxicity
Daphnia acute toxicity
Alga growth inhibition test
Ready biodegradation

Estimates using EPI Suite (US EPA):
Melting point
Adsorption/desorption
Probability of ready biodegradation

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
Canadian New Substances Notification (2005)
Korean New Substances Notification (2005)
United States Environmental Protection Agency (2005)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Component 3 (Mixed sulfonic acid, calcium salts) (contains <70% notified chemical). The notified chemical and those in STD 1200 and 1201 are referred to as XC6170. The difference between the notified chemicals is the length of an alkyl chain.

3. COMPOSITION

DEGREE OF PURITY
High.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as part of a lubricant additive package.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	10-100	10-100	10-100	10-100	10-100

USE
The notified chemical is part of a lubricant additive package that will be used as a detergent additive at 1-5% concentration in lubricants for automotive and diesel engine crankcase oils, air and water-cooled two-cycle engine oils, industrial oils, hydraulic fluids and gear oils.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne

TRANSPORTATION AND PACKAGING
The notified chemical will be transported either by ship and offloaded to tank trucks or rail cars for distribution to a blending facility or by drum shipped directly to the customer. After blending, the finished lubricant will be transported in 1-4 L containers, drums or tank trucks.

5.2. Operation description

Reformulation

At the blending site the additive package (containing <70% notified chemical) is transferred from drums or rail cars into storage tanks. Transfer of the additive package from the tank trucks to storage tanks will be via a 10 cm hosing.

Transfer from storage tanks to blend tanks is automated with computer-controlled valves. The additive package is blended with other components to form the finished lubricant (1-5% notified chemical). The blending process occurs in a closed system and is computer controlled. The blended lubricant is transferred automatically to a storage tank. The finished lubricants are then packaged for shipment in 1-4 L containers, drums, or bulk tank trucks.

The small container-processing machine is fully automated with a worker watching to ensure the filling mechanism properly enters the containers. The drumming facility uses automated weight scales to fill the drums, with a worker watching to ensure the drum filling mechanism properly enters the drum before the drum is filled. The operators manually apply bungs and labels to filled drums. A transfer hose is used for bulk tank truck filling.

The finished lubricants are transported for use commercially (70%) or to service stations and retail outlets (30%). The lubricants are transported in the following manner: 50% in drums, 40% in 1-4 L containers and 10% in bulk tank trucks.

Commercial end users:
Some of the 1-4 L containers (10% of the total volume of the imported chemical) and the drums (50% of the total volume of the imported chemical) will be sold to commercial automotive engine service outlets (i.e. auto repair shops). A pneumatic pump will be inserted into the drum and used to transfer the lubricant. In many cases, stationary engines will be routinely lubricated using dedicated lubricating oil reservoirs and piping to add lubricants directly without human intervention. For non-stationary automotive applications, workers will check lubricant levels in the engine manually and top off, as needed using lubricant added via pneumatic delivery systems. Most of the commercial end users will recycle their used oil obtained from engine oil drains occurring during routine maintenance and repair work.

The bulk product (10% of the total volume of the imported chemical) will be sold to high volume commercial end users, such as truck and taxi fleets, where it will be used to lubricate petrol and diesel engines. It is assumed that engines lubricating process is similar as discussed in the paragraph above.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Analysing additive package on arrival	1	10 mins	30 d/yr
Unloading tanks trucks and drums	1-2	30 mins	30 d/yr
Sampling finished oil	1-2	10 mins	220 d/yr
Loading finished oil into tank trucks	1-2	30 mins	220 d/yr
Commercial end users	>1000	8 hours	220 d/yr

Exposure Details

Warehousing and transport:
The workers would only be exposed to the notified chemical in the case of accidental rupture of the containers.

Reformulation:
At blending sites, the notified chemical is transferred from drums, rail cars and tank trucks into storage tanks. During connection and disconnection of lines, incidental skin contact from splashes, drips and spills is possible. Connection of the hose during transfer from tank trucks takes 10 minutes. An air back flush system is used to prevent spillage during this process.

Transfer from storage tanks to blend tanks is automated with computer-controlled valves. The

blending process occurs in a closed system and is computer controlled, thus, there should be minimal exposure during this stage. The blended lubricant is transferred automatically to a storage tank before packaging for transport. The blending facilities are well ventilated, with control systems for accidental spills and wastewater treatment.

Workers may be exposed to the finished lubricant (containing the notified chemical at 1-5%) during the filling operations. The 1-4 L container-packaging machine is fully automated and worker exposure may occur when the filling mechanism does not properly enter the container. The drumming facility uses automated weight scales to fill the drums, however, worker exposure may occur if the drum filling mechanism does not properly enter the drum. Exposure may also occur when the workers put on bungs and labels. Transfer of the finished product from storage tanks to bulk containers can cause dermal exposure to workers by way of drips and spills of blended lubricant. An air flush system is used to prevent spillage during this process. Workers' exposure during transfer/filling will be minimised by the use of PPE such as gloves, eye protection, protective clothing and hard hats.

Laboratory staff takes samples of the notified chemical in the additive package as well as the blended oil products for testing. During sampling and analysis of the additive package the most likely worker exposure is via skin contact. However, minimal exposure will occur during the laboratory testing since it will take only a few minutes per batch.

Commercial end users:
Workers may be exposed to the notified chemical at up to 5% in the finished lubricant product during engine maintenance and during transfer of lubricant product from containers to engines, mainly via dermal contact. In the industrial and commercial environment, engines are maintained by professional mechanics, who are likely to wear appropriate PPE and have access to engineering controls.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The chemical will be transferred from rail car, tank trucks or drums to on-site holding tanks. A special air back flush system prevents any spillage. It is expected that the residue of the notified chemical contained in the drums will be 0.1%. Empty drums are steam cleaned with the resultant aqueous waste sent to on-site wastewater facilities. Assuming that the chemical is 70% pure and that 10% is delivered by drum, then it is estimated that 7 kg of the notified chemical will be sent to the wastewater treatment plant per year, based on the maximum import of 100 tonnes of notified chemical. The wastewater treatment separates 90% of the oil with further treatment of the wastewater removing a further 80%, resulting in 0.14 kg per annum being released by this route.

Rail car and tank trunks containing the chemical are likely to be refilled without flushing to the extent practicable or be rinsed by licensed contractor with disposal by incineration. The blending of the chemical with lubricating oil will occur in fully enclosed automated systems. Blending tanks are rinsed with lubricating oil with the rinseate recycled back into the blending system or disposed by incineration.

In the unlikely event of an accident, the spillage will be contained within concrete bunds and either reclaimed or sent to on-site wastewater treatment facilities where residual hydrocarbon based products will be separated from the aqueous stream by the American Petroleum Industry (API) process, with a claimed removal of greater than 95%. The aqueous waste undergoes further treatment involving pond aeration and biological treatment before being released to the sewage system. The remaining oily waste will be incinerated. As a result of these processes, the accidental release from transport of the additive package and finished oils is unlikely to be significant.

RELEASE OF CHEMICAL FROM USE
Virtually no release will result from transport of the finished lubricant, as the dedicated tank trucks are simply refilled and are rarely cleaned. Some minor and diffuse exposure will result from spills during addition of oil to vehicles and from oil leaks from engines. It is also expected that 0.1% of the finished product containing the notified chemical will remain in drums or 1 - 4 L containers. Drums are expected to be used for 50% of the finished product. Therefore, of the total 100 tonnes containing up to 70% pure chemical, 35 tonnes will be will transported as finished product in drums. It is expected that 0.1% will remain in drums meaning that 35 kg will be sent to waste water treatment during drum

recycling. During water treatment, 90% of the oil containing the product is separated with the oil sent for recycling and the waste water containing 3.5 kg of notified chemical sent for further waste water treatment. The waste water is subjected to biological treatment and filtration removing a further 80% of the chemical. Consequently, 0.7 kg per annum is expected to be released to waterways via this route. For the 1 – 4 L containers, which will be used for 40% of the packaging, it is expected, using the above assumptions, that 28 kg will remain as residue. This is likely to be disposed as domestic waste. However, the greatest potential for exposure is through disposal of waste oil containing the additive.

A survey by the Australian Institute of Petroleum (AIP 1995) indicates that of the annual sales of automotive engine oils in Australia, some 60% are potentially recoverable (ie not burnt in the engines during use). This report also indicates that around 86% of oil changes take place in specialised automotive service centres, where old oil drained from crankcases could be expected to be disposed of responsibly - either to oil recycling or incineration. The remaining 14% are removed by "do it yourself" (DIY) enthusiasts, and in these cases some of the used oil would be either incinerated, left at transfer stations where it is again likely to be recycled, or deposited into landfill. A recent report estimated that DIY activities account for between 7 to 10% of the unaccounted used oil (MEINHARDT 2002).

According to a survey tracing the fate of used lubricating oil in Australia (Snow 1997) only around 20% of used oil removed by enthusiasts is collected for recycling, approximately 25% is buried or disposed to landfill, 5% is disposed of into stormwater drains and the remaining 50% unaccounted for.

Consequently, assuming that oil removed by professional mechanics is disposed of appropriately (ie sent for recycling or possibly burning as workshop heating oil), negligible release of the notified chemical should result from these professional activities. During recycling it is expected that most of the chemical will decompose and any remainder will report to the asphalt portion.

Assuming that 14% (14 tonnes) of the used oil is removed by the DIY enthusiasts it is possible to have 20% (2.8 tonnes) collected for recycling, 25% (3.5 tonnes) buried or disposed to landfill, 5% (700 kg) disposed into stormwater drains and 50% (7 tonnes) unaccounted for.

Since gear oil and hydraulic fluid changes are likely to be carried out by specialists, and will be disposed of more appropriately, an amount less than 1% of the total import volume of the notified substance could be expected to enter the aquatic environment via disposal into the storm water system. Since the use of the lubricating oils will occur throughout Australia, all releases resulting from use or disposal of used oil will be very diffuse, and release of the notified chemical in high concentrations is very unlikely except as a result of transport accidents.

Although a listed potential use is for water cooled marine engines including two stroke engines, in actuality the notifier indicates that this is unlikely to occur. Therefore there will be no likely release to the aquatic environment via this route.

5.5. Disposal

Drums are sent to drum recyclers where they are steam cleaned and water is sent to wastewater treatment. It is assumed 0.1% of the notified chemical remains after use. Small containers sold to consumers are likely to be sent to landfill.

5.6. Public exposure

The public will not be exposed to the notified chemical during storage, transport or reformulation except in the event of an accident or spill.

The small containers (1-4 L) of lubricants containing up to 55 of the notified chemical (30% of the total volume of the imported chemical) will be sold to service stations and the general public. Public exposure to the notified chemical may occur during do-it-yourself replenishment of lubricant through spills, splashes and contact with runs or drips on the outside of the container after filling. Exposure is also possible while handling automotive components that have been in contact with the lubricant. The most likely route of public exposure is by skin contact, with the possibility of ocular and inadvertent oral exposure. It is unlikely that PPE will be worn.

6. PHYSICAL AND CHEMICAL PROPERTIES

Some experimental data on an analogue of the notified chemical (OLOA 249SX in 30% mineral oil) have been provided, with other values estimated using EPI Suite (US EPA). The measured values were for Pour Point, Boiling Point Range, Density, Vapour Pressure, Water Solubility and Octanol/Water Partition Coefficient.

Appearance at 20ºC and 101.3 kPa Dark brown viscous liquid (notified chemical is never isolated from reaction mixture)

Melting Point Pour point = -18 ºC
METHOD ASTM D 5950
Remarks Measured using a automatic pour point apparatus.

Estimated using EPI Suite to be 290 – 323ºC
TEST FACILITY Chevron Energy Technology Company (2006)

Boiling Point 348 ºC - 735ºC
METHOD OECD TG103
Remarks The range is for 40.8% recovered mass. The method is High Temperature Simulated Distillation similar to ASTM D 6352.

Boiling Point was also estimated using EPI Suite to be 667 – 736ºC at 101.3 kPa
TEST FACILITY Chevron Energy Technology Company (2006)

Density 1223 kg/m^3 at 20ºC
METHOD OECD TG109
Remarks Determined with an oscillating densitometer.
TEST FACILITY Chevron Energy Technology Company (2006)

Vapour Pressure 2.8 x 10^{-7} kPa at 20ºC
METHOD OECD TG104
Remarks The Maxwell-Bonnell calculation was used in conjunction with a correlation from distillation data.

Estimated using EPI Suite to be 3.61 x 10^{-22} – 1.68 x 10^{-19} kPa at 25ºC
TEST FACILITY Chevron Energy Technology Company (2006)

Water Solubility < 2.1 x 10^{-5} g/L
Remarks Shake flask method as column elution method unsuitable for petroleum additives.

Estimated from log Kow using EPI Suite to be 3.11 x 10^{-10} – 3.58 x 10^{-7} mg/L at 25ºC

Hydrolysis as a Function of pH Not measured.
Remarks The notified chemical is unlikely to hydrolyse as there are no hydrolysable groups present.

Partition Coefficient (n-octanol/water) log P_{ow} > 7.4
METHOD OECD TG117
Remarks Measured using HPLC.

log Pow was estimated using EPI Suite to be 10.95-13.89 and indicates strong preference for the octanol phase.
TEST FACILITY Chevron Energy Technology Company (2006)

Adsorption/Desorption Not measured.
Remarks Log K_{oc} was estimated using EPI Suite to be 7.99 – 10.16 and indicates a preference for adsorption to soils.

Dissociation Constant Not measured.
Remarks The notified chemical is an anionic chemical which is expected to be fully dissociated under normal environmental conditions.

Particle Size Not measured.
Remarks Not applicable, as the notified chemical never isolated from the reaction mixture.

Flash Point Not measured.
Remarks Estimated from an analogous chemical to be 150°C

Flammability Limits Not measured.

Autoignition Temperature Not measured.

Explosive Properties Not expected to be explosive.

Reactivity
Remarks May react with strong oxidising agents, such as chlorates, nitrates and peroxides. Hazardous polymerisation will not occur.

7. TOXICOLOGICAL INVESTIGATIONS

The following data have been provided for analogous chemical in different concentrations in mineral oil that are considered to be acceptable analogues of the notified chemical. The concentrations are:

- Analogue A - 50% weight in a highly refined mineral oil
- Analogue B - 54% weight in a highly refined mineral oil
- Analogue C - 43% weight in a highly refined mineral oil
- Analogue D - 55-61% weight in a highly refined mineral oil
- Analogue E - 55-61% weight in a highly refined mineral oil (with a different trade name)
- Analogue F - 44% weight in a highly refined mineral oil
- Analogue G - Analogue F at various concentrations in petrolatum
- Analogue H – 70% weight in a highly refined mineral oil

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 >5000 mg/kg bw (Analogue A, D)	low toxicity
Rat, acute dermal LD50 >5000 mg/kg bw (Analogue A, D)	low toxicity
Rat, acute inhalation toxicity	not performed
Rabbit, skin irritation (Analogue A, E, H)	severely irritating (analogue A), moderately irritating (analogue E), slightly irritating (analogue H)
Rabbit, eye irritation (Analogue A, E)	slightly irritating
Guinea pig, skin sensitisation – non-adjuvant test (Analogue B, E, F, G)	evidence of sensitisation
Skin sensitisation (human patch test) (Analogue D)	non-irritating and no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days (Analogue A, C)	no NOEL established, NOAEL 150 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days (Analogue A)	no NOEL established
Reproductive toxicity – one generation study. (Analogue E)	NOEL >500 mg/kg bw/day
Genotoxicity – bacterial reverse mutation (Analogue A, D)	non mutagenic
Genotoxicity – In vitro Mammalian Chromosome Aberration Test (Analogue A)	non genotoxic
Genotoxicity – in vivo mouse micronucleus assay (Analogue A, D)	non genotoxic

7.1.a. Acute toxicity – oral

TEST SUBSTANCE Analogue A

METHOD OECD TG 401 Acute Oral Toxicity – Limit Test
Species/Strain Rat/Crl:CD(SD)BR
Vehicle None
Remarks - Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	5000	0

LD50 >5000 mg/kg bw
Signs of Toxicity Five males and one female exhibited dark-stained urogenital area and/or nonformed faeces/soft stool within 3 days of exposure. No signs of toxicity were observed 4 days after treatment.
Effects in Organs No abnormal findings observed at gross necroscopy examination at termination.
Remarks - Results None.

CONCLUSION The analogue chemical is of low toxicity via the oral route.

TEST FACILITY Covance Laboratories Inc (1998a)

7.1.b. Acute toxicity – oral

TEST SUBSTANCE Analogue D

METHOD OECD TG 401 Acute Oral Toxicity – Limit Test.
EC Directive 92/69/EEC B.1 Acute Toxicity (Oral) – 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	5/sex	5004	0

LD50 >5004 mg/kg bw
Signs of Toxicity None
Effects in Organs None
Remarks - Results None

CONCLUSION The analogous chemical is of low toxicity via the oral route.

TEST FACILITY Pharmakon (1997a)

7.2.a. Acute toxicity – dermal

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test
Species/Strain	Rat/Crl:CD(SD)BR
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	5/sex	5000	0

LD50	>5000 mg/kg bw
Signs of Toxicity - Local	Dermal irritation was observed in all animals, consisting of moderate to severe erythema, slight to moderate oedema, and slight atonia, desquamation, coriaceousness, fissuring, and subcutaneous haemorrhaging. This irritation was still present in three female animals at day 14.
Signs of Toxicity - Systemic	Four females exhibited weight loss of 4-9 g during the first week.
Effects in Organs	No significant findings.
Remarks - Results	None.
CONCLUSION	The analogue chemical is of low toxicity via the dermal route.
TEST FACILITY	Covance Laboratories Inc (1998b)

7.2.b. Acute toxicity – dermal

TEST SUBSTANCE	Analogue D
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – 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	5/sex	2006	0

LD50	>2006 mg/kg bw
Signs of Toxicity - Local	None
Signs of Toxicity - Systemic	One treated female showed low body weight gain, however, this is likely incidental.
Effects in Organs	None
Remarks - Results	None
CONCLUSION	The analogous chemical is of low toxicity via the dermal route.
TEST FACILITY	Pharmakon (1997b)

7.3. Acute toxicity – inhalation

Not performed. The notified chemical has a low vapour pressure. Hence inhalation exposure to the notified chemical is not likely to be of concern.

7.4.a. Irritation – skin

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White albino
Number of Animals	6 per study
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	Two studies were conducted, using 6 animals each. In the first study the test substance was washed off using soap/water following the 4-hour exposure period, and some residue remained. In the second study the test substance was washed off with mineral oil and soap/water, which removed more of the test material. Data from both tests are presented here.

RESULTS

Study 1 – washed with soap/water

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema	3.1	4	14 days	1
Oedema	3.3	4	7 days	0

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

Study 2 - washed with mineral oil and soap/water

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema	2.6	3	7 days	0
Oedema	3.3	4	7 days	0

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

Remarks - Results	The majority of animals in both studies showed blanching for 72 hours. Desquamation and/or fissuring were seen in all animals in both groups at day 7, and in three animals in Study 1 on day 14. Five animals in study 1 had areas of possible necrosis after 96 hours.
CONCLUSION	The analogue chemical is severely irritating to the skin.
TEST FACILITY	Covance Laboratories Inc (1998c)

7.4.b. Irritation – skin

TEST SUBSTANCE	Analogue E
METHOD	0.5 mL of test substance was applied to three clipped, intact areas on the back of each of six rabbits for four hours under occlusive dressings. After exposure, the exposed areas were wiped with mineral oil. Irritation was scored at 1, 24, 48 and 72 hours and 7 and 14 days, using a modified Draize scoring method.
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	None
Observation Period	14 days
Type of Dressing	Occlusive
Remarks - Method	None

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	1.93	4	7 days	0
Oedema	0.15	2	72 hours	0

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

Remarks - Results	After 1 hour, all animals exhibited well defined to moderate erythema. Over the next 48 hours, the severity of the irritation was reduced in only one animal, and progressed to severe erythema and eschar in one animal. At 72 hours, two animals exhibited severe erythema and eschar, with the other animals exhibiting slight to moderate erythema. At seven days the worst-affected animal still displayed well-defined erythema, which cleared after 14 days. All animals had dry/flaky skin at 72 hours and/or 7 days.
CONCLUSION	The analogous chemical is moderately irritating to the skin.
TEST FACILITY	CEHC (1989a)

7.4.c Analogue H

TEST SUBSTANCE	Analogue in 30% mineral oil
METHOD	US EPA Health Effects Test Guidelines, OPPTS 870.2500, Acute Dermal Irritation (1998).
Species/Strain	Rabbit/New Zealand White albino
Number of Animals	3
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	No protocol deviations during 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	0.3	0.3	0.3	1	24 hours	0
Oedema	0	0	0	0		

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

Remarks - Results	The primary skin irritation index was 0.5. At 1 hr, all animals display slight erythema. By 24 hrs dermal irritation resolved.
CONCLUSION	The analogue chemical is slightly irritating to the skin.
TEST FACILITY	Charles River Laboratories (2006)

7.5.a. Irritation – eye

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	9
Observation Period	72 hours
Remarks - Method	The eyes of 3 rabbits were flushed with water for 1 minute starting 30 seconds after test material instillation. The eyes of the other 6 rabbits

remained unflushed.

RESULTS

Flushed

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.44	2	48 hours	0
Conjunctiva: chemosis	0.33	1	24 hours	0
Conjunctiva: discharge	0	3	1 hour	0
Corneal opacity	0	0	0	0
Iridial inflammation	0	0	0	0

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

Unflushed

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.39	2	48 hours	0
Conjunctiva: chemosis	0.33	2	24 hours	0
Conjunctiva: discharge	0	2	1 hour	0
Corneal opacity	0	0	0	0
Iridial inflammation	0	0	0	0

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

Remarks - Results: Positive irritation reactions were seen in all six animals with unwashed eyes, including: diffuse, deep crimson conjunctival redness, with individual vessels not easily discernable; obvious conjunctival swelling with partial eversion of the lids; and discharge with moistening of the lids and hairs just adjacent to the lids (at 1 hour). By the 24-hour observation, the discharge had cleared, and only mild conjunctival redness and chemosis were observed. All effects had cleared by 48 hours, except for one animal that presented mild conjunctival redness.

Flushing of the eye is not consistent with the test guidelines, and thus these results have not been analysed in detail but the flushing appeared to have little effect.

CONCLUSION: The analogue chemical is slightly irritating to the eye.

TEST FACILITY: Covance Laboratories Inc (1998d)

7.5.b. Irritation – eye

TEST SUBSTANCE: Analogue E

METHOD: 0.1 mL of test substance was applied to the conjunctival sac of one eye of each of nine rabbits. After a 30-second exposure, the eyes of three rabbits were washed with water for one minute. Irritation was scored at 1, 24, 48 and 72 hours, using a modified Draize scoring method.

Species/Strain: Rabbit/New Zealand White
Number of Animals: 9
Observation Period: 72 hours
Remarks - Method: No significant protocol deviations.

RESULTS

Treated-unrinsed

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0	3	1 hour	0
Conjunctiva: chemosis	0	1	1 hour	0
Conjunctiva: discharge	0	3	1 hour	0

Corneal opacity	0	0	0	0
Iridial inflammation	0	0	0	0

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

Treated-rinsed

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0	3	1 hour	0
Conjunctiva: chemosis	0	1	1 hour	0
Conjunctiva: discharge	0	2	1 hour	0
Corneal opacity	0	0	0	0
Iridial inflammation	0	0	0	0

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

Remarks - Results: All effects had a maximum duration of 1 hour.

CONCLUSION: The analogous chemical is slightly irritating to the eye.

TEST FACILITY: CEHC (1989b)

7.6.a. Skin sensitisation

TEST SUBSTANCE: Analogue B

METHOD: OECD TG 406 Skin Sensitisation - Buehler test.
Species/Strain: Guinea pig/Dunkin Hartley
PRELIMINARY STUDY: Maximum Non-irritating Concentration:
topical: None found.
MAIN STUDY
Number of Animals: Test Group: 10/sex Control Group: 10/sex
INDUCTION PHASE: Induction Concentration:
topical: undiluted
Signs of Irritation: Erythema scores of 1-2 were seen in all animals.
CHALLENGE PHASE
1st challenge: topical: 5% in mineral oil
2nd challenge

Remarks - Method: No significant protocol deviations.

RESULTS

Remarks - Results: Eighteen out of 20 animals showed grade 2 skin reactions at challenge and 20 out of 20 animals showed grade 1 skin reactions at challenge.

CONCLUSION: There was evidence of reactions indicative of skin sensitisation to 0.5% analogue chemical under the conditions of the test.

TEST FACILITY: Hill Top Biolabs (1994)

7.6.b. Skin sensitisation – 5% challenge

TEST SUBSTANCE: Analogue F

METHOD: OECD TG 406 Skin Sensitisation – Buehler test
EC Directive 96/54/EC B.6 Skin Sensitisation - Buehler test
Species/Strain: Guinea pig/Hartley
Vehicle: Mineral oil
PRELIMINARY STUDY: Maximum Non-irritating Concentration:
None determined. Maximum score at 0.5% (w/v) was 1.
MAIN STUDY

Number of Animals	Test Group: 10/sex	Control Group: 10/sex
INDUCTION PHASE	Induction Concentration: Topical: 100%	
Signs of Irritation	Erythema, up to score 2.	
CHALLENGE PHASE		
1st challenge	Topical: 5%	
2nd challenge	Topical: 5%	
3rd challenge	Topical: 0.5%	
Remarks - Method	No significant protocol deviations.	

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions* after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	5%	17/20	19/20	19/20	19/20
	0.5%			8/20	15/20
Control Group	5%	0/10	0/10	0/10	0/10
	0.5%			0/10	0/10

*Animals with a response of 2 or more.

Remarks - Results	Controls exhibited scores of 1, at most. Animals scored as positive at challenge or rechallenge had scores of 2 or more.
CONCLUSION	There was evidence indicative of skin sensitisation to the analogue chemical under the conditions of the test.
TEST FACILITY	HTR (1995)

7.6.c. Skin sensitisation – various % challenge

TEST SUBSTANCE	Analogue G (75, 50, 25 and 10% in petrolatum)			
METHOD	40 CFR 792, US EPA FIFRA and TSCA 40 CFR 792 Good Laboratory Practice Standards			
Species/Strain	Guinea pig/Hartley			
Vehicle	Petrolatum			
PRELIMINARY STUDY	Maximum Non-irritating Concentration: None determined.			
MAIN STUDY				
Number of Animals	Test Group: 5 groups of 20 females		Control Group: 6 groups of 10 females as concurrent initiation controls for either challenge or rechallenge and one group of 10 for vehicle control.	
INDUCTION/ CHALLENGE PHASE	Induction Concentration: Topical			
	Test	Induction (%)	Challenge (%)	Re-challenge (%)
	1	10	5	1
	2	25	5	1
	3	75	25	No rechallenge
	4	50	25	10
	5	50	1	No rechallenge
	6	Vehicle (100)	Vehicle (100)	Vehicle (100)
Signs of Irritation	Erythema, up to score 2.			
Remarks - Method	No significant protocol deviations.			

RESULTS

Animal	*Number of Animals Showing Skin Reactions* after:*			
	1st challenge		*2nd challenge*	
	24 h	*48 h*	*24 h*	*48 h*
Test 1	20/20	14/20	20/20	12/20
Control Group	0/10	1/10	1/10	0/10
Test 2	16/20	5/20	10/20	13/20
Control Group	0/10	0/10	1/10	0/10
Test 3	17/20	14/20		
Control Group	1/10	0/10		
Test 4	7/20	7/20	9/20	11/20
Control Group	2/10	0/10	0/10	0/10
Test 5	7/20	10/20		
Control Group	0/10	0/10		
Test 6 (vehicle)	0/10	0/10	0/10	0/10

*Animals with a response of 2 or more.

Remarks - Results: Controls exhibited scores of 1, at most. Animals scored as positive at challenge or rechallenge had scores of 2 or more.

CONCLUSION: There was evidence indicative of skin sensitisation to the analogue chemical under the conditions of the test.

TEST FACILITY: HTR (1993)

7.6.d. Skin sensitisation – 50% challenge

TEST SUBSTANCE: Analogue E

METHOD: OECD TG 406 Skin Sensitisation – Buehler test
EC Directive 96/54/EC B.6 Skin Sensitisation - Buehler test

Species/Strain: Guinea pig/Hartley
Vehicle: Mineral oil
PRELIMINARY STUDY: Maximum Non-irritating Concentration:
None determined. Maximum score at 0.5% (w/v) was 1.
MAIN STUDY
Number of Animals: Test Group: 10/sex Control Group: 5/sex
INDUCTION PHASE: Induction Concentration:
Topical: 100%
Signs of Irritation: Erythema, up to score 2.
CHALLENGE PHASE
1st challenge: Topical: 50%
Remarks - Method: No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions* after:*	
		1st challenge	
		24 h	*48 h*
Test Group	50%	4/20	7/20
Control Group	50%	0/10	0/10

*Animals with a response of 2 or more.

Remarks - Results: Controls exhibited scores of 1, at most. Animals scored as positive at challenge or rechallenge had scores of 2 or more.

CONCLUSION	There was evidence indicative of skin sensitisation to the analogue chemical under the conditions of the test.
TEST FACILITY	HTR (1991)

7.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Analogue D
METHOD	
Study Design	Pilot phase: Test substance was applied undiluted, and at 50%, 25% and 10% in mineral oil. 0.2 mL was applied under occlusive dressing, for 24 hours. Induction Procedure: Nine consecutive applications of 0.2 mL undiluted test substance under occlusive dressing for 24 hours each. Rest Period: 14 days. Challenge Procedure: Application of 0.2 mL of test substance to a naïve location under occlusive dressing for 24 hours.
Study Group	101 subjects between 21 and 60 years old.
Vehicle	None
Remarks - Method	Nineteen subjects completed a one week pilot phase to determine the appropriate concentration to be used in the main study and continued on with the main study.
RESULTS	
Remarks - Results	One subject was discontinued from the test due to pruritis on the left arm, which was regarded by the consulting dermatologist as unrelated to exposure to the test product. No other significant irritation was observed. There was no evidence of sensitisation in the test.
CONCLUSION	A repeat insult patch test was conducted using undiluted analogous chemical under occlusive dressing. The analogous chemical was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	CRTC (1991)

7.8.a. Repeat dose toxicity – 28 day- Screening study

TEST SUBSTANCE	Analogue A
METHOD	EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Crl:CD BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Corn oil
Remarks - Method	No recovery period was used.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5/sex	0	0

II (low dose)	5/sex	200	0
III (mid dose)	5/sex	1000	0
IV (high dose)	5/sex	2000	0

Clinical Observations

Transient salivation after dosing was noted intermittently throughout the study among high-dose rats of both sexes. Bodyweight gain was variable and did not reveal any treatment related trends. Increased food consumption was observed for mid- and high-dose females, which reflected the increased bodyweight gain for these groups.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Increased white blood cell parameters were noted among high-dose females. Increased alanine aminotransferase, aspartate aminotransferase, glucose, phosphorous, and reduced cholesterol were noted for both sexes in the mid- and high-dose groups compared with control. There was some evidence of increased urea nitrogen for males, especially in the high-dose group.

Effects in Organs

Liver weight was increased in all treated female groups.

In the stomach, roughening of the epithelial aspect was observed in 2/5 high-dose rats and 3/5 mid-dose rats of either sex. Yellow staining of the epithelial aspect was seen in 1/5 high-dose rats of either sex, and 1/5 mid-dose rats of either sex. Epithelial hyperplasia and hyperkeratosis in the nonglandular stomach, sometimes with associated inflammatory changes, was reported for all rats of either sex in the mid- and high-dose groups, and in 1/5 low-dose female rats.

Remarks – Results

Elevated white blood cell parameters may have been due to the inflammatory responses seen in the stomach. The changes to blood chemistry and increased liver weight suggest a perturbation in liver function.

CONCLUSION

The No Observed Effect Level could not be established from this study, based on the epithelial hyperplasia and hyperkeratosis in the nonglandular stomach seen in one female receiving a dose of 200 mg/kg/day. The test was used to determine the dose level for the main 90-day study (0, 10, 100, 500 mg/kg/day).

TEST FACILITY Huntington Life Sciences Ltd. (1999)

7.8.b Repeat dose toxicity - 28 days

TEST SUBSTANCE Analogue C

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: 14 days
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10/sex	0	0
II	10/sex	50	0
III	10/sex	150	0
IV	10/sex	500	0
V	10/sex	1000	0
VI (control recovery)	10/sex	0	0

VII	10/sex	1000	0

Mortality and Time to Death
None

Clinical Observations
Significantly lower body weight gain was noted in males receiving 500 and 1000 mg/kg bw/day, with overall weight gain being 9% and 6% lower than controls at the end of treatment. Food consumption was also significantly decreased in group 4 males during week 3.

The differences seen between groups in the functional observation battery were not dose related and were not considered to be treatment related.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Platelet counts were significantly increased on day 28 in males receiving 500 and 1000 mg/kg bw/day. This is unlikely to be toxicologically relevant as abnormalities in platelet count generally manifest as decreases.

Gamma-glutamyl transferase (GGT) was significantly increased in males in all treated groups, however this was thought to be the result of an abnormally low concentration observed in the control group.

Serum alanine amino transferase (ALT) was significantly increased on day 28 in high-dose males (52%) and females receiving 500 and 1000 mg/kg bw/day (108% and 144%), and increased (not significantly) by 42% in 500 mg/kg bw/day males and 36% in 150 mg/kg bw/day females. These changes were not supported by changes to other indicators of hepatic injury.

Phosphorus was significantly increased by 9% in 1000 mg/kg bw/day males. This was considered incidental in the absence of any related findings.

Other changes to hematology and blood chemistry did not show a dose response, or occurred in the recovery period only, and were not considered to be treatment related.

Effects in Organs
The most notable findings at the day 28 necroscopy involved the stomach:

Group	*50 mg/kg bw/day*	*150 mg/kg bw/day*	*500 mg/kg bw/day*	*1000 mg/kg bw/day*
Males	-	-	(2/5) Thickening (2/5) Minimal oedema of submucosa	(4/5) Thickening (2/5) Minimal/mild oedema of submucosa (3/5) Minimal epithelial hyperplasia
Females	(1/5) Thickening	(1/5) Thickening (1/5) Foci (2/5) Minimal oedema of submucosa	(1/5) Thickening (1/5) Foci (1/5) Ulcer, mild oedema of submucosa, minimal haemorrhage, minimal epithelial hyperplasia, mild inflammation	(1/5) Thickening (1/5) Minimal oedema of submucosa (2/5) Minimal epithelial hyperplasia

There were no notable findings in the stomachs of animals after the recovery period, or in control animals.

The liver-to-body weight ratio was significantly increased in 1000 mg/kg bw/day males (19%) and 500 and 1000 mg/kg bw/day females (11% and 20% respectively). There were no unusual microscopic findings in the livers of any animals.

Thymus weights were decreased in 1000 mg/kg bw/day males. This was considered to be incidental in the absence of any related findings.

Minimal to mild pulmonary irritation was seen at day 28 in one male and two females receiving 1000 mg/kg bw/day, and in three males and one female after the recovery period. This irritation most likely arises from a foreign body response to incidentally aspirated test article.

Other changes to organs did not show a dose response relationship, and were not considered to be treatment related.

Remarks – Results
The main toxicologically relevant findings were related to irritation of the stomach. One female receiving 500 mg/kg bw/day had severe stomach irritation, including an ulcer.

There was also some evidence of test-substance-related changes to the liver (increased liver weight, increased serum ALT). These were statistically significant in both sexes at 500 mg/kg bw/day and above, with non significant trends in serum ALT at 150 mg/kg bw/day. However there were no microscopic findings or supporting blood chemistry findings, and there was full recovery, indicating that these were most likely adaptive changes.

Body weight gain and food intake was slightly decreased in high dose males.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study, based on a stomach ulcer and related findings in one female treated with 500 mg/kg bw/day.

TEST FACILITY SLI (2002)

7.9. Repeat dose toxicity – 90 day (main study)

TEST SUBSTANCE Analogue A

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
EC Directive 88/302/EEC B.26 Subchronic Oral Toxicity Test: 90-Day Repeated Oral Dose Study using Rodent Species.

Species/Strain	Rat/Crl:CD BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: 28 days
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10/sex	0	1
II (low dose)	10/sex	10	1
III (mid dose)	10/sex	100	0
IV (high dose)	10/sex	500	1
V (control recovery)	10/sex	0	0
VI (high dose recovery)	10/sex	500	0

Mortality and Time to Death
Three animals were sacrificed due to a damaged eye, following the blood sampling procedures in week 13. These deaths were not related to the treatment.

Clinical Observations
Salivating after dosing was noted intermittently primarily among high-dose rats of either sex from week 5 onwards.

During week 1 of the treatment period, there was an unusually high bodyweight gain for mid-dose females, but in isolation this is not considered to be of toxicological importance. During the recovery period, a statistically significant higher bodyweight gain and higher food consumption was seen in males.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

A number of statistically significant changes were observed in mid- and high-dose animals. The following table summarises these observations:

	Low dose	*Mid dose*	*High dose*	*High dose recovery*
Potassium	(m) 7% increase, p<0.05 (f) no significant change.	(m) 7% increase, p<0.05 (f) no significant change.	(m) 7% increase, p<0.01 (f) no significant change.	No observed change
Glucose	(m) 7% increase, not significant (f) 2% increase, not significant	(m) 11% increase, not significant (f) 9% increase, not significant	(m) 15% increase, p<0.05 (f) 14% increase, p<0.01	(m) 6% increase, not significant (f) 12% increase, P<0.05
Cholesterol	(m) No observed change (f) 11% decrease, not significant	(m) 15% decrease, p<0.05 (f) 9% decrease, not significant	(m) 25% decrease, p<0.01 (f) 30% decrease, p<0.01	(m) 5% decrease, not significant (f) 7% decrease, not significant
Sodium	No observed change	(m) 2% increase, p<0.01 (f) 1% increase, p<0.05	(m) 2% increase, p<0.01 (f) 1% increase, p<0.01	No observed change
Chlorine	No observed change	(m) 1% increase, p<0.01 (f) 1% increase, p<0.05	(m) 3% increase, p<0.01 (f) 3% increase, p<0.01	No observed change
Calcium	No observed change	(m) 4% decrease, p<0.01 (f) 2% decrease, p<0.05	(m) 6% decrease, p<0.01 (f) 3% decrease, p<0.01	No observed change
Alkaline phosphatase	No observed change.	No observed change	(m) 24% increase, p<0.05 (f) 17% increase, not significant	No observed change
Alanine amino transferase	No observed change	No observed change.	(m) 67% increase, p<0.01 (f) 32% increase, p<0.01	No observed change
Total protein	No observed change	No observed change	(m) 6% decrease, p<0.05 (f) 4% decrease, p<0.05	No observed change

Creatine was significantly reduced in high-dose males only.
A/G ratio was significantly increased in high dose males only.

Minor variations in haematology were either not dosage related or influenced by outlier animals and are not thought to be toxicologically significant.

Effects in Organs

Upon necroscopy, there were a number of effects observed in the stomach. These are summarised below:

	Low dose	*Mid dose*	*High dose*	*High dose recovery*
Thickened forestomach	(m) 0/10 (f) 0/10	(m) 0/10 (f) 0/10	(m) 5/10 (f) 0/10	(m) 0/10 (f) 0/10
Roughened forestomach	(m) 0/10 (f) 0/10	(m) 3/10 (f) 5/10	(m) 9/10 (f) 7/10	(m) 0/10 (f) 0/10
Epithelial hyperplasia and hyperkeratosis	(m) 1/10 (f) 0/10	(m) 7/10 (f) 8/10	(m) 9/10 (f) 9/10	(m) 1/10 (f) 2/10
Epithelial erosion	(m) 0/10 (f) 0/10	(m) 0/10 (f) 2/10	(m) 1/10 (f) 2/10	(m) 0/10 (f) 0/10
Subepithelial inflammation	(m) 0/10 (f) 0/10	(m) 2/10 (f) 3/10	(m) 8/10 (f) 10/10	(m) 0/10 (f) 0/10
Submucosal inflammation	(m) 0/10 (f) 0/10	(m) 3/10 (f) 3/10	(m) 8/10 (f) 10/10	(m) 0/10 (f) 0/10

A dosage related and statistically significant increase in kidney weight was noted for all male groups in comparison with the controls. This finding was not correlated with any microscopic changes.

At termination, raised liver weights were noted for high-dose males in comparison with the control, and minimal centrilobular hepatocyte hypertrophy was also seen in the livers of this group. This finding was not noted in any other groups, or following the recovery period.

A statistically significant higher spleen weight was noted for high-dose males and mid- and high-dose females in comparison with the controls. This finding was not correlated with any microscopic changes.

Other inter-group differences in organ weights were not considered to be toxicologically important, due to the absence of statistical significance, consistent dose response relationships or supporting histological lesions.

Aggregations of vacuolated histiocytes were recorded in the mesenteric lymph nodes of all animals of both sexes in the high-dose group, and in 3 females given in the mid-dose group, and this finding persisted following the recovery period.

Granulomatous inflammation was recorded in the paracortex of 9 male and 7 female rats in the high dose group at the end of the main study, and was seen at a reduced level following the recovery period.

Neurobehavioural parameters

The analogous chemical did not cause any behavioural changes that were considered to be indicative of neurotoxicity.

Remarks – Results

A No Observed Effect Level (NOEL) could not be determined due to minor stomach lesion seen in one male rate in the low dose. This lesion was attributed to local irritation effect rather than systemic toxicity. Adverse effects to the stomach were the most pronounced dose related findings, and were severe and widespread in mid- and high-dose animals. These effects were most likely due to local irritation caused by the analogue chemical, and are consistent with the skin irritation study.

The changes to the liver, kidney and the altered blood chemistry were likely adaptive.

The causes of the changes to the mesenteric lymph node are difficult to identify, but may indicate toxicity to histiocytes and/or macrophages. The aggregations of vacuolated histiocytes may be due to histiocytes/macrophages ingesting the substance and subsequently accumulating in the mesenteric lymph node, or alternatively the substance may have been absorbed into the lacteals and only ingested by histiocytes on arrival at the draining lymph node. The granulomatous inflammation may be due direct inflammation

caused by the substance, or by toxicity to macrophages and a subsequent inflammatory reaction. These effects are not considered to provide evidence of serious systemic toxicity.

CONCLUSION
The No Observed Effect Level (NOEL) could not be established in this study.

TEST FACILITY Huntington Life Sciences Ltd. (2000)

7.10. Toxicity to reproduction – one generation study

TEST SUBSTANCE Analogue E

METHOD OECD TG 415 Reproductive toxicity test
Species/Strain Rat/Sprague-Dawley
Route of Administration Oral – gavage
Exposure Information Exposure period - female: At least 14 days prior to mating through lactation day 20.
Exposure period - male: At least 70 days prior to mating
Vehicle Corn oil
Remarks – Method No significant protocol deviations.

RESULTS

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

Mortality and Time to Death
None

Effects on Parental (P) animals:
Slightly decreased mean absolute weight and mean relative to body weight for the epididymides at 500 mg/kg bw/day. In the absence of any other findings, this was not considered toxicologically relevant.

Other changes did not show any dose response relationship and thus were not considered to be treatment related.

Effects on 1st Filial Generation (F1)
Any changes did not show any dose response relationship and thus were not considered to be treatment related.

Remarks – Results
None

CONCLUSION
The No Observed Effect Level (NOEL) for reproductive effects was established as 500 mg/kg bw/day in this study, based on no significant findings at any dose level.

TEST FACILITY SLI (2004)

7.11.a. Genotoxicity – bacteria

TEST SUBSTANCE Analogue A

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure
Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2*uvr*A

Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 33.3-10,000 µg/plate b) Without metabolic activation: 33.3-10,000 µg/plate
Vehicle	DMSO
Remarks - Method	The tester strain WP2*uvr*A was retested as the positive control in the initial test did not reach an acceptable (3-fold greater than the vehicle) level of revertant colonies.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	None	None	At ≥ 3,300 µg/plate	Negative
Test 2	None	None	At ≥ 3,300 µg/plate	Negative
Present				
Test 1	None	None	At ≥ 2,500 µg/plate	Negative
Test 2	None	None	At ≥ 2,500 µg/plate	Negative

Remarks - Results	Positive control substances had the appropriate response, except for WP2*uvr*A in the presence of S9, which was retested and an acceptable positive control value obtained. Negative controls were within historical limits.

CONCLUSION	The analogue chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Covance Laboratories Inc (1998e)

7.11.b.Genotoxicity – bacteria

TEST SUBSTANCE	Analogue D
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 97/69/EC Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2*uvr*A
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction
Concentration Range in Main Test	a) With metabolic activation: 100, 250, 500, 1000, 5000, 10000 µg/plate b) Without metabolic activation: 100, 250, 500, 1000, 5000, 10000 µg/plate
Vehicle	None
Remarks - Method	No significant protocol deviations

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	None	None	≥ 1000µg/plate	None
Test 2		None	≥ 1000µg/plate	None
Present				
Test 1	None	None	≥ 1000µg/plate	None
Test 2		None	≥ 1000µg/plate	None

Remarks - Results	Positive control substances had the appropriate response. Negative controls were within historical limits.

CONCLUSION	The analogous chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	CHV (1997)

7.12. Genotoxicity – in vitro

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Human lymphocytes
Metabolic Activation System	Aroclor 1254 induced rat liver S9fraction.
Vehicle	DMSO
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	34.7, 49.5, 70.7, 101, 144*, 205*, 293*, 419, 598, 854, 1220, 1740, 2480, 3540, 5050 µg/mL	3 h	22 h
Test 2	12.5, 25, 50, 100, 150*, 200*, 250*, 300, 350, 400 µg/mL	19.3 h	22 h
Test 3	12.5, 25*, 50*, 100*, 150, 200, 250, 300, 350, 400 µg/mL	43.3 h	46 h
Present			
Test 1	34.7, 49.5, 70.7, 101*, 144*, 205*, 293, 419, 598, 854, 1220, 1740, 2480, 3540, 5050 µg/mL	3 h	22 h
Test 2	25*, 50*, 100*, 150, 200*, 250*, 300* µg/mL	3 h	22 h
Test 3	25*, 50*, 100*, 150, 200, 250, 300 µg/mL	3 h	46 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 419 µg/mL	≥ 854 µg/mL	Negative
Test 2	≥ 250 µg/mL	-	Negative
Test 3	≥ 200 µg/mL	-	Negative
Present			
Test 1	≥ 419 µg/mL	≥ 854 µg/mL	Negative
Test 2	≥ 250 µg/mL	-	Negative
Test 3	≥ 250 µg/mL	-	Negative

Remarks - Results	Mitomycin C and Cyclophosphamide were used as positive controls and showed distinct increases in cells with structural chromosomal aberrations. Negative controls were within historical limits.
CONCLUSION	The analogue chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Covance Laboratories Inc (1998f)

7.13.a. Genotoxicity – in vivo

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/Crl:CD-I(ICR)BR
Route of Administration	Intraperitoneal injection
Vehicle	Peanut oil
Remarks - Method	No significant protocol deviations.

The doses were determined based on 2 preliminary toxicity experiments.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	6/sex	-	48
IIm (low dose)	6/m	47	24
IIIm (mid dose)	6/m	94	24
IVm (high dose)	6/m	188	24
Vm (high dose 48 hour)	6/m	188	48
Iif (low dose)	6/f	63	24
IIIf (mid dose)	6/f	125	24
IVf (high dose)	6/f	250	24
Vf (high dose 48 hour)	6/f	250	48
VI (positive control, CP)	6/sex	20	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	Males: 2 animals receiving 94 mg/kg exhibited rough haircoat 24 hours after dosing. All animals dosed with 188 mg/kg were hypoactive and had rough haircoat at 24 hours. Three males in this group were found dead at 48 hours. Females: 3 animals receiving 125 mg/kg exhibited rough haircoat 24 hours after dosing. All animals dosed with 250 mg/kg were slightly hypoactive, with hunched position and rough haircoat at 24 hours. Three females in this group were found dead at 48 hours.
Genotoxic Effects	The test article was not cytotoxic to the bone marrow.
Remarks - Results	The positive control group induced statistically significantly increases in micronucleated polychromatic erythrocytes. Negative controls were within historical limits.

CONCLUSION The notified chemical was not clastogenic under the conditions of this in vivo mouse micronucleus assay.

TEST FACILITY Covance Laboratories Inc (1998g)

7.13.b.Genotoxicity – in vivo

TEST SUBSTANCE Analogue D

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.

Species/Strain	Mouse/Crl:CD-1(ICR)BR
Route of Administration	Intraperitoneal injection
Vehicle	Peanut oil
Remarks - Method	No significant protocol deviations.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5/sex	0	24, 48, 72 hours
II (low dose)	5/sex	625	24, 48, 72 hours
III (mid dose)	5/sex	1250	24, 48, 72 hours
IV (high dose)	5/sex	2500	24, 48, 72 hours
V (positive control, CP)	5/sex	60	24 hours

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	Animals receiving 625 mg/kg bw were slightly hypoactive at 72 hours.

	Animals receiving 1250 mg/kg bw were slightly hypoactive with rough haircoats at 48 hours (males only) and 72 hours (all animals). Animals receiving 2500 mg/kg bw were slightly hypoactive at 24 hours, hypoactive with rough haircoats at 48 hours, and very hypoactive with rough haircoats, laboured breathing and distended abdomens at 72 hours. Two animals receiving 2500 mg/kg bw died during the test. Bone marrow cytotoxicity was pronounced in animals receiving 2500 mg/kg bw and there was some evidence of bone marrow toxicity in animals receiving 1250 and 625 mg/kg bw.
Genotoxic Effects	None
Remarks - Results	The positive control group induced statistically significantly increases in micronucleated polychromatic erythrocytes. Negative controls were within historical limits. The notified chemical did not induce a stastically significant increase in bone marrow polychromatic erythrocytes under the conditions of the test.
CONCLUSION	The analogous chemical was not clastogenic under the conditions of this in vivo mouse micronucleus test.
TEST FACILITY	CHV (1996)

8. ENVIRONMENT

8.1. Environmental fate

The following data have been provided for Analogue A, Analogue C and Analogue E, which are considered to be acceptable analogues of the notified chemical.

8.1.1.a. Ready biodegradability

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test. US EPA Method 796.3260
Inoculum	Activated sludge from Prospect Bay Wastewater Treatment Facility
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Carbon analyser
Remarks - Method	The test was performed to measure the amount of CO_2 produced from the biodegradation of the test substance and express it as a % of the theoretical amount of CO_2 that could have been produced if complete biodegradation occurs. The test consisted of a control for the background measurement of the CO_2 production of the inoculum, a reference (canola oil) at 10 mg C/L and a treatment group at a concentration of 10 mg C/L. Each group contained triplicate test chambers. The CO_2 produced is measured using a carbon analyser. The CO_2 were removed for analysis on days 2, 6, 9, 13, 19, 23 and 29. The temperature and pH measured during the test were within acceptable limits.

RESULTS

Test substance		*Canola oil*	
Day	*Cumulative % of theoretical CO_2 evolved*	*Day*	*Cumulative % of theoretical CO_2 evolved*
2	0	2	1
6	2	6	30

13	8	13	66
19	10	19	78
23	12	23	80
29	14	29	83

Remarks - Results: The average cumulative % of theoretical CO_2 produced by the test substance was 12.5% over the exposure period of 29 days. Thus it is considered not readily biodegradable. The reference substance yielded >60% of theoretical maximum CO_2 prior to day 14 of the test thereby fulfilling the criteria for a valid test. The amount of CO_2 evolved by the control did not exceed the 17 mg/L value which is the acceptable limit for CO_2 evolution tests.

CONCLUSION: The test substance is considered not readily biodegradable.

TEST FACILITY: Wildlife International Ltd (1998)

8.1.1.b. Ready biodegradability

TEST SUBSTANCE: Analogue E

METHOD: OECD TG 301D Ready Biodegradability: Closed Bottle Test.
EEC Directive 79/831 and EEC Directive 67/548 Annex V C6.

Inoculum: Activated sludge from the HRC Limited sewage treatment plant
Exposure Period: 28 days
Auxiliary Solvent: None
Analytical Monitoring: COD
Remarks - Method: The test consisted of inoculated, inoculated with filter paper and non-inoculated controls; two references, aniline and sodium benzoate at 2 and 3 mg/L, respectively, and a treatment group at a concentration of 2 mg/L. Dissolved oxygen concentrations for each test medium were determined in duplicate at 0, 5, 15 or 28 days by means of a Yellow Springs BOD probe and COD were measured by using a semi-micro sample digestion method.

RESULTS

Test substance		*Sodium benzoate*		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*	*Day*	*% Degradation*
5	5	5	87	5	57
15	3	15	85	15	59
28	8	28	97	28	61

Remarks - Results: The test substance attained 8% biodegradation after 28 days and thus is considered not readily biodegradable. Sodium benzoate and aniline attained 97% and 61% degradation, respectively, within 28 days. Thus both references fulfil the criteria for a valid test. Oxygen depletion in the inoculated and non-inoculated control series were within the acceptable limits.

CONCLUSION: The test substance is not considered to be readily biodegradable.

TEST FACILITY: Huntingdon Research Centre (1989)

8.1.2. Bioaccumulation

The notified chemical may have potential to bioaccumulate as it has a high calculated log Kow of 10.95 - 13.89 but a low Bio-Concentration Factor (BCF) of 70.79 (BCFWIN v2.15.

8.2. Ecotoxicological investigations

8.2.1.a. Acute toxicity to fish

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 203 Fish, Acute Toxicity Test –Semi-static
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	44 mg $CaCO_3$/L
Analytical Monitoring	TOC analysis
Remarks – Method	The test material was prepared as a Water Accommodated Fraction (WAF) due to its expected low water solubility. The mixtures were stirred at room temperature for 24 h and allowed to settle for 4 h. Following the settling period the water phase containing the WAF was removed with a siphon. The 1,000 mg/L test solutions were slightly cloudy at the start of each 24 h period and they were clear with a thin film on the surface at the end of each 24 h. No other insoluble material was noted in any test vessels. The WAF was prepared at the beginning of the test and three additional times during the test to allow media renewal at approximately 24, 48 and 72 h. A range-finding test was conducted at the WAF concentrations of 10, 100 and 1,000 mg/L. The definitive test was conducted under static renewal conditions only at the highest concentration. Ten fish were allocated to each of three replicates of the control and treatment at the WAF concentration of 1000 mg/L. The number of surviving organisms and the presence of sublethal effects were determined visually after 2, 24, 48, 72 and 96 h. Total organic carbon (TOC) analyses were performed at 0 and 24 h, with no significant change compared to control, though levels were low (2.7-5.5 mg C/L). The pHs, temperatures, conductivities and dissolved oxygen concentrations were within acceptable levels.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*				
Nominal		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
1,000*	10	0	0	0	0	0
Control	10	0	0	0	0	0

*Tests were performed in triplicates each containing 10 fish.

LC50	>1000 mg/L nominal WAF at 96 hours.
NOEC	1000 mg/L nominal WAF at 96 hours.
Remarks – Results	All organisms of the control and the treatment at 1,000 mg/L survived the 96 h toxicity test. No sub lethal effects were noted at 96 h.
CONCLUSION	The test substance is considered to be non-toxic to fish up to the limit of its water solubility.
TEST FACILITY	Wilbury T. R. Laboratories Inc. (1998a)

8.2.1.b. Acute toxicity to fish

TEST SUBSTANCE	Analogue E
METHOD	1985 EPA/TSCA Part 797 – Environmental effects testing guidelines, Subpart B – Aquatic Guidelines, Section 797.1440 fish acute toxicity test – under static renewal conditions.
Species	Rainbow trout (*Oncorhyricus mykiss*)
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	36-38 mg $CaCO_3$/L
Analytical Monitoring	Carbon analyser

Remarks – Method

The test material was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. The mixtures (see below) were stirred at room temperature for 20 h and allowed to settle for 1 h. Following the settling period the WSF, separated from floating or settled test material, was removed with a siphon. Throughout the test period, a film of undissolved test material was observed on the surface of all test solutions.

Based on the results of the range-finding test, the definitive test was conducted at nominal concentrations of 1000, 600, 360, 220 and 130 mg/L WSF. Twenty fish were allocated to each of treatment groups and control. The number of surviving organisms and the presence of sublethal effects were determined visually after 0, 3, 6, 24, 48, 72 and 96 h. Total organic carbon (TOC) analyses were performed at 0 and 24 h, with control ranging from 6.2-7.7 mg/L and treatment groups ranging from 40-92 mg/L. The pHs and dissolved oxygen concentrations were within acceptable levels during the test.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*					
Nominal		*3h*	*6h*	*24h*	*48h*	*72h*	*96h*
1000[a]	20	0	0	0	0	0	0[b]
600	20	0	0	0	0	0	0
360	20	0	0	0[c]	0	0	0
220	20	0	0	0	0	0	0
130	20	0	0	0	0	0	0
Control	20	0	0	0	0	0[d]	0[d]

a Test solutions were noted to have a heavy layer of film present on the surface at 48, 72 and 96 h of exposure
b One of the surviving fish exhibited darkened pigmentation
c Several of the surviving fish exhibited darkened pigmentation
d A total of 19 fish were observed in the control vessels

LC50 >1000 mg/L nominal WSF at 96 h
NOEC 1000 mg/L nominal WSF at 96 h
Remarks – Results All organisms of the control and the treatment groups survived the 96 h toxicity test. Sub lethal effects of darkened pigmentation were noted at nominal WSF concentrations of 360 and 1000 mg/L WSF at 24 and 96 h, respectively.

CONCLUSION The test substance is considered to be non-toxic to fish up to the limit of its water solubility.

TEST FACILITY Springborn Laboratories Inc (1989)

8.2.2.a. Acute/chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Analogue A

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test
Species *Daphnia magna*
Exposure Period 48 h
Auxiliary Solvent None
Water Hardness 164-168 mg $CaCO_3$/L
Analytical Monitoring TOC analysis
Remarks - Method The WAFs were prepared according to the procedures in the fish test. A range-finding test was conducted at the WAF concentrations of 1, 10, 100 and 1,000 mg/L. The definitive test was conducted under static conditions at the WAF of 1,000 mg/L. Ten daphnia were allocated to each of the three replicates treatment and control. The number of surviving organisms and the presence of sublethal effects were determined visually

after 24 and 48 h. Total organic carbon (TOC) analyses were performed at 0 and 24 h, with no significant change compared to control, though levels were low (1.8-2.1 mg C/L). The pHs, temperatures, conductivities and dissolved oxygen concentrations were within acceptable levels.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*Number Dead*	
		24 h	*48 h*
1,000*	10	1	1
	10	1	1
	10	0	0
Control	10	0	0

* Three replicates each containing 10 daphnia

LC50	>1000 mg/L at 48 hours (nominal WAF)
NOEC	1000 mg/L at 48 hours (nominal WAF)
Remarks - Results	No insoluble material was noted during the test. 97% survival with no sublethal effects occurred in the control.

CONCLUSION The test substance is considered to be non-toxic to *Daphnia magna* up to the limit of its water solubility.

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

8.2.2.b. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Analogue E

METHOD 1985 EPA/TSCA Part 797 – Environmental effects testing guidelines, Subpart B – Aquatic Guidelines, Section 797.1300 Daphnid acute toxicity test – under static renewal conditions.

Species	*Daphnia magna*
Exposure Period	48 h
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	Carbon analyser
Remarks - Method	The WSFs were prepared according to the procedures in the fish test. Based on the results of the range-finding test, a definitive test at nominal concentrations of 130, 220, 370, 600 and 1,000 mg/L WSF was conducted. Twenty daphnia were allocated to each of control and treatment groups in duplicate (ten daphnids per replicate). The number of surviving organisms and the presence of sublethal effects were determined visually after 0, 3, 6, 24 and 48 h. Total organic carbon (TOC) analyses were performed at 0 and 24 h, with no significant change compared to control (7.3-11.5 mg C/L). The pHs and dissolved oxygen concentrations were within acceptable levels.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*Immobilization (%)*			
		3 h	*6 h*	*24 h*	*48 h*
1000	20	0^{abc}	25^{bcde}	60^{ab}	75^{ch}
500	20	0	0	0	0^{c}
250	20	0	0	25	30^{ci}
125	20	0	0	0^{bf}	0^{cg}
63	20	0	0	0	0^{cg}
Control	20	0	0	0	0

a All of the surviving daphnia were lethargic

b A film was present on the surface of the test solution
c Test solutions were cloudy
d All of the surviving daphnids were lethargic and caught on particulate matter
e A precipitate was observed at the surface of the test solution
f One of the surviving daphnids was lethargic
g Several of the surviving daphnids were observed at the surface of the test solution
h All of the surviving daphnids were caught on particulate matter
i One of the surviving daphnids was observed at the surface of the test solution

LC50	830 mg/L nominal WSF at 48 h (CI: 130-1000 mg/L)
NOEC	<63 mg/L nominal WSF at 48 h
Remarks - Results	75% immobilisation was observed at nominal concentration of 1000 mg/L WSF. Immobilisation of 30% was observed at 250 mg/L WSF while no immobilised organisms were observed in the remaining concentrations tested. All surviving daphnids at 1000 mg/L WSF were observed to be caught on particulate matter. Several surviving daphnids at concentrations ≤ 250 mg/L WSF were observed at the surface of the test solution. Test solutions at test termination, except for control, were all observed to be cloudy. The 48 h EC50 of 830 mg/L WSF was estimated by non-linear interpolation.
CONCLUSION	The test substance is considered to show some toxicity to *Daphnia magna* below the limit of its water solubility. However, these results should be treated with caution as it appears the toxic effects observed are a result of physical effects.
TEST FACILITY	Springborn Laboratories Inc. (1990)

8.2.3.a. Algal growth inhibition test

TEST SUBSTANCE	Analogue A
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	Freshwater alga (*Selenastrum capricornutum*)
Exposure Period	96 h
Concentration Range	1000 mg/L
Auxiliary Solvent	None
Water Hardness	Not given
Remarks - Method	The WAF was prepared in a similar manner as the fish test. Based on the range-finding test, the definitive test was conducted for 96 h under static conditions using dilution water control and the WAF of 1,000 mg/L. Approximately 10,000 algal cells/mL were allocated into each of three replicates of the treatment and control. The number of algal cells/mL in each test vessel and the occurrence of relative size differences, unusual cell shapes, colours, flocculations, adherence of cells to test containers, or aggregation of cells was determined visually using a haemocytometer. Cell counts were made and recorded daily during the 96 h duration. Total organic carbon (TOC) analyses were performed at 0 and 96 h, with no significant change compared to control, though levels were low (1.2-2.8 mg C/L). Temperatures and pHs were within acceptable limits during the test.

RESULTS

Biomass		*Growth*	
Nominal (WAF) E_bC50 mg/L at 96 h	*Nominal (WAF) NOE_bC mg/L at 96 h*	*Nominal (WAF) E_rC50 mg/L at 96 h*	*Nominal (WAF) NOE_rC mg/L at 96 h*
>1000	1000	>1000	1000

Remarks - Results	The 24, 48, 72 and 96 h EC50 were >1000 mg/L when calculated using biomass or growth rate. Similarly, the 96 h NOEC was calculated to be 1000 mg/L. No effects (size differences, unusual cell shapes, colours, flocculations, adherence of cells to test containers, or aggregation of

cells) were noted during the test.

CONCLUSION The test substance is considered to be non-toxic to alga up to the limit of its water solubility.

TEST FACILITY Wilbury T. R. Laboratories Inc. (1998c)

8.2.3.b. Algal growth inhibition test

TEST SUBSTANCE Analogous chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test Static Test. No test data were provided but reference to the following literature values were provided: http://www.epa.gov/chemrtk/alklsulf/c13206tp.pdf

Species	Freshwater alga (*Selenastrum subcapitata*)
Exposure Period	96 h
Concentration Range	1000 mg/L
Auxiliary Solvent	None
Water Hardness	Not given
Remarks - Method	The WAF was prepared.

RESULTS

Biomass EL50 mg/L	*Growth* EL50 mg/L
> 1000	> 1000

8.2.4.a. Inhibition of microbial activity

TEST SUBSTANCE Analogue A

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated sludge obtained from the municipal wastewater treatment plant
Water hardness	<4 mg $CaCO_3$/L
Exposure Period	3 h
Concentration Range	650 - 10,000 mg/L
Remarks – Method	Based on the range-finding test performed at concentrations of 10, 100, 500 and 1,000 mg/L, the definitive test was conducted under static conditions for 3 h. Nominal concentrations of 0 (control), 650, 1,300, 2,500, 5,000 and 10,000 mg/L were prepared by the addition of the test substance directly to the dilution water. After 3 h incubation period the concentrations of the dissolved oxygen was measured. The test was performed using 3 nominal concentrations of the reference, 3,5-dichlorophenol at 5, 12 and 30 mg/L.

RESULTS

IC50	>10,000 mg/L
NOEC	10,000 mg/L
Remarks – Results	Insoluble material was observed floating on the surface of the test media in all non-control test vessels in the test. The EC50 for the reference was 9.0 mg/L and within the acceptable range of 5-30 mg/L. The test substance did not inhibit respiration of the activated sludge for the concentration range tested. The 3 h EC50 could not be calculated by standard statistical techniques as the % inhibition was <50% of the control at all concentrations tested.

CONCLUSION The test substance is not inhibitory to the activated sludge micro-organisms.

TEST FACILITY Wilbury T. R. Laboratories Inc. (1998d)

8.2.4.b. Inhibition of microbial activity

TEST SUBSTANCE	Analogue C
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sludge was obtained from the wastewater treatment plant
Exposure Period	3 h
Concentration Range	Nominal: 100, 300 and 1000 mg/L
Remarks – Method	The test was conducted under static conditions. Nominal concentrations were prepared by the addition of the test substance directly to the dilution water derived from the dechlorinated tap water. After 3 h incubation period the concentrations of the dissolved oxygen was measured. The test was also performed using 3,5-dichlorophenol as the reference.
RESULTS	
IC50	>1000 mg/L (nominal)
NOEC	1000 mg/L (nominal)
Remarks – Results	Insoluble material was observed on the bottom and on the surface of non-control test vessels. The EC50 for the reference was 9.0 mg/L and within the acceptable range of 5-30 mg/L. The test substance did not inhibit respiration of the activated sludge for the concentration range tested. The 3 h EC50 could not be calculated by standard statistical techniques as the % inhibition was <50% of the control at all concentrations tested.
CONCLUSION	The test substance is not inhibitory to the activated sludge micro-organisms.
TEST FACILITY	Wilbury Laboratories Inc. (1994)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical will be imported and reformulated into lubricant oils at the blending facilities. The used oil and the sludge collected from the on-site wastewater treatment facilities may be incinerated. This will likely generate water vapour and oxides of carbon and calcium oxide. The main environmental exposure is expected to result from inappropriate disposal of waste lubricant product, assuming a worst case scenario of about 14% of oil changes in Australia are performed by DIY enthusiasts.

This disposal is however, widespread across Australia. Most of the improperly released notified chemical due to DIY activities is likely to become associated with soils or sediments, as will the notified chemical released to landfill as container residues. The notified chemical released into the aquatic environment would be expected to become associated with the sediments due to its estimated low water solubility. While some components of the notified chemical are not readily degradable, these can be expected to slowly degrade due to the biotic and abiotic processes.

The amount released to stormwater drains (less than 1% of the import volume) can enter the aquatic compartment and could be expected to become associated with suspended organic material (due to the calculated high Pow), settle out into the sediments and eventually be biodegraded.

It is difficult to estimate the Predicted Environmental Concentration (PEC) of the notified chemical released into the stormwater drains, which have the potential to directly enter the aquatic environment. However, a worst case estimated PEC might be calculated if it is assumed that all of the 1% of the notified chemical that is expected to be released into the stormwater (i.e. 1 tonne) drains into a single metropolitan area with a geographical footprint of 500 square

kilometres and an average annual rainfall of 500 mm. With a maximum annual release into this localised stormwater system of 1000 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 4 µg/L. It should be stressed that this result is very much a worst case scenario, and that in reality releases of the chemical would be very much more diffuse than indicated here, and also at significantly reduced levels.

9.1.2. Environment – effects assessment

Based on the ecotoxicity data provided, the notified chemical is not toxic up to the limit of water solubility where the TOC = 1.2–9.2 mg/L. A PNEC is not able to be calculated based on the TOC value.

9.1.3. Environment – risk characterisation

The notified chemical is not toxic to the aquatic organisms tested up to the limit of its water solubility where the TOC = 1.2-9.2 mg/L This value allows for a safety factor well in excess of the 100, required when toxicity data are available for three species, and when compared with the PEC of 4 µg/L. Further, the low water solubility of the notified chemical and its limited release to the aquatic environment (mainly via stormwater drainage) can expect to reduce the possibility of sufficient amounts to remain in solution to cause acute toxicity. The notified chemical is expected to become associated with the sediments, and biodegradation will further reduce the risk to the aquatic life.

Overall, the environmental risk from the proposed blending and use of the notified chemical is expected to be low.

As the notified chemical forms a component of an oil based product, which in itself poses a risk to the aquatic environment, the product should be prevented from entering waterways.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Warehouse and transportation workers would only be exposed to the notified chemical in the case of accidental rupture of containers.

During blending of the lubricant additive into the final lubricant product, the main exposure will be from drips and spills during transfer into storage tanks through hoses and lines, and during filling of the finished lubricant into containers and drums and containers. During the rest of the operation there is unlikely to be exposure, as the process is automated and enclosed. Exposure may also occur when workers put bungs or labels on drums and containers. Laboratory workers may also be exposed during quality testing.

About 70% of the lubricant products (containing <5% notified chemical) will be sold to commercial users. There is potential for exposure to skin during transfer of lubricant or during its use. These users will likely be professional mechanics and engineers, and use either pneumatic device to transfer oil, or have access to engineering controls and use of PPE. Exposure to the notified chemical is expected to be low, based on these controls, and the low concentration of the notified chemical in the products.

9.2.2. Public health – exposure assessment

Approximately 30% of the final lubricant product will be sold to service stations and consumer users, therefore, public exposure will be widespread. The lubricant will be used to manually top up and fill engines in cars, lawn mowers etc. Dermal exposure, and possible ocular, and inadvertent oral exposure to the notified chemical may occur when the lubricant oil is added and drained from engines and when handling components that have come into contact with the oil. DIY end users are not likely to wear PPE while using the engine oil. It is expected that exposure to individuals will be intermittent, and the concentration (<5%) of the notified chemical within the oil will limit the total exposure levels.

The public may also be exposed to the notified chemical from spills onto roads, parking areas and soil. However, exposure will be limited by the dispersive use and low concentration of the

notified chemical in products.

9.2.3. Human health – effects assessment

All toxicity studies provided were conducted using analogous chemicals which are accepted.

In four Buehler skin sensitisation tests, challenges to previously exposed rats resulted in markedly increased skin reactions compared with naïve controls. Based on this evidence, the notified chemical is classified in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2002) as:

R43 - May cause sensitisation by skin contact.

In a dermal irritation test using an analogous chemical (Analogue A), a number of signs of dermal irritation were seen, persisting in all animals for more than 7 days. In the second dermal irritation test the analogue chemical (E) is a moderate skin irritant, with mean draize score for erythema of 1.93. Erythema formation was classed as > 2 in 2/6 animals tested. However, the notifier performed a skin irritation study using a commercial batch of another analogue (notified as STD/1196) as opposed to an experimental batch of an analogue on the basis that severe dermal irritation was not typical of this class of chemicals and could be explained by incomplete neutralisation, a final step in the manufacture. The notified chemical was slightly irritating to skin. A human repeat insult occlusive patch test (Analogue D) found no evidence of irritation.

A NOEL could not be determined from repeat dose oral toxicity studies (Analogue A) (28 day preliminary and 90 day main). The animals in the 90-day test exhibited changes to blood chemistry, increased liver and kidney weights, lesions in the stomach, and aggregations in the mesenteric lymph node. However, these changes are not considered to be signs of serious systemic toxicity. The second 28 day repeat-dose oral toxicity study found that the chemical (Analogue D) was irritating to the stomach, but no other conclusive signs of systemic toxicity were observed. A NOAEL of 150 mg/kg bw/day was established based on the stomach irritation. Based on this data the classification as 'R48 – Danger of serious damage to health by prolonged exposure' is not required.

The analogue chemicals were of low acute toxicity via oral and dermal routes, and were slightly irritating to eyes.

No adverse effects were observed in a one generation reproductive toxicity study, with the NOAEL established as 500 mg/kg bw/day (Analogue D).

There was no evidence of genotoxicity based on the following tests: bacterial reverse mutation, *in vitro* mammalian chromosome aberration test and *in vivo* mouse micronucleus assay.

Based on the available data, the notified chemical is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2002).

9.2.4. Occupational health and safety – risk characterisation

The lubricant additive package (<70% notified chemical) that is imported into Australia is hazardous specifically it may cause skin sensitisation. However, the risk to workers will be mitigated by the mainly automated transportation and formulation process of the additive package. Exposure is not expected, except via splashes and spills, and it is expected that PPE will minimise exposure.

Commercial users will use the final product containing 1-5% of the notified chemical. They are likely to have minimal exposure to the formulated lubricants as they use pneumatic transfer equipment and personal protective equipment, such as gloves, overalls and work boots. The OHS risk presented by the notified chemical is expected to be low in situations where the workers take precautions to reduce dermal exposure. Commercial users are likely to take precautions that are recommended on the label/MSDS. As the MSDS for the lubricating oil carries a risk phrase for skin sensitisation, workers will be warned and adequate skin protection is recommended.

Based on the concentration of the notified chemical in the finished product, the risk of skin sensitisation exists, especially at workplaces with a low level of control mechanisms.

9.2.5. Public health – risk characterisation

Consumer users of the lubricants containing the notified chemical are unlikely to take precautions to minimise exposure. Thus, they will have intermittent dermal exposure, and possibly accidental ocular and oral exposure, to the notified chemical.

There is a high risk of dermal sensitisation for people who use the lubricants containing 1-5% of the notified chemical without PPE. Therefore, advice to consumers needs to be highlighted on the label.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. The classification and labelling details are:
R43 – May cause sensitisation by skin contact

As a comparison only, the classification of 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
Skin Sensitisation	1	May cause an allergic skin reaction

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described, based on the expected low exposure.

10.3.2. Public health

There is High Concern to public health when used as a lubricant additive due to the hazardous nature and proposed use patterns.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the lubricant additive package containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the lubricant additive package containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the

responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following hazard classification for the notified chemical:

  – R43 May cause sensitisation by skin contact

- The following risk phrases for products/mixtures containing the notified chemical apply:
  – ≥1% R43 May cause sensitisation by skin contact

- Products containing ≥1% notified chemical should carry the following warnings on the label:
  – S2 Keep out of reach of children
  – S24 Avoid contact with skin
  – S36 Wear suitable protective clothing
  – S37 Wear suitable gloves

- The National Drugs and Poisons Standing Committee (NDPSC) should consider the notified chemical for listing on the SUSDP.

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe practices to minimise occupational exposure during handling of the notified chemical as introduced:
  – Minimise spills and drips
  – Where possible, automated processes should be used to reduce worker contact
  – Use closed systems for reformulation

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced and as diluted for use in the lubricant product:
  – Chemical resistant gloves
  – Protective clothing
  – Safety goggles

  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 NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Public Health

- The marketers of lubricants containing 1% or more the notified chemical should indicate on the product label that the product may cause skin sensitisation (allergic skin reaction) and that skin contact should be avoided.

Disposal

- The notified chemical should be disposed of by authorised landfill or incineration.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by preventing spills entering waterways, using physical containment, followed by absorption onto inert material (vermiculite, sand etc) and placed into suitable containers for disposal.

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act:
  – if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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