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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Chemical A in BP Turbo Oil 2380

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

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

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

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BP Australia Pty Ltd (ABN 53 004 085 616)
132 McCredie Road
Guildford, NSW 2161

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular formula, structural formula, molecular weight, spectral data, analogue details, degree of purity, concentration in products, impurities, introduction volume and details of use.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant, particle size, flammability limits, mammalian toxicity data and ecotoxicity data.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None known

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Chemical A in BP Turbo Oil 2380
Hatcol 1510

MOLECULAR WEIGHT
Majority >500 Da

ANALYTICAL DATA
Reference IR and GC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 90% for Chemical A (notified chemical) and B (STD/1235) together in BP Turbo Oil 2380

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -20.2 ± 0.5°C	Measured
Boiling Point	> 400 ± 0.5°C at 99.97 kPa	Measured
Density	946 kg/m^3 at 20.4 ± 0.5°C	Measured
Vapour Pressure	5.4 × 10^{-12} kPa at 25°C	Measured
Water Solubility	< 3.22 × 10^{-4} g/L at 20 ± 0.5°C	Measured

Hydrolysis as a Function of pH	> 1 year at pH 4, 7, 9 at 25°C	Measured
Partition Coefficient (n-octanol/water)	log P_{OW} = > 6.50 at 20°C	Measured
Adsorption/Desorption	log K_{oc} > 5.63	Measured
Dissociation Constant	Not determined	The notified chemical does not contain dissociable functionality.
Flash Point	223 ± 2ºC at 101.3 kPa	Measured/Estimated/Calculated/Analogue data/MSDS
Flammability	Not determined	Based on the low vapour pressure and the high flash point the notified chemical is not expected to be highly flammable.
Autoignition Temperature	394 ± 5ºC	Measured
Explosive Properties	Not explosive	Estimated based on the chemical structure
Oxidising Properties	Not oxidising	Estimated based on the chemical structure

DISCUSSION OF PROPERTIES
The notified chemical is not a dangerous good based on the above physical and chemical properties.
For full details of tests on physical and chemical properties, please refer to Appendix A.

Reactivity
Stable under normal conditions of use, does not react with air or water.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported as a component of a finished aviation turbine oil (< 70% of notified chemical) in 1 L cans. There will be no reformulation or repackaging of the turbine oil.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	10-30	10-30	10-30	10-30	10-30

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
BP Australia Pty Ltd.
132 McCredie Rd
Guildford NSW 2161

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as component of finished turbine oil (BP Turbo Oil 2380) in 1 L cans. The notified chemical will be transported and stored in these containers prior to use. The turbine oils containing the notified chemical will be transported to end use sites on pallets by road or rail.

USE
The notified chemical is a component (<70%) of aviation turbine oil.

OPERATION DESCRIPTION
The notified chemical will be imported in a finished product. There will be no manufacture, reformulation or repackaging of the turbine oil containing the notified chemical in Australia. The turbine oil will be warehoused prior to transport to commercial customers around Australia.
The turbine oil containing the notified chemical will be used by Licensed Aircraft Maintenance Engineers to charge and top up aircraft machinery. The method of charging and topping up aircraft machinery is for the most part a manual process.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	4	5	60
Storage workers	4	1	60
Licensed aircraft maintenance engineers	2000	2	100

EXPOSURE DETAILS
Transport and warehouse personnel will only be exposed to the notified chemical in case of an accident involving the breach of the import containers.

End users are unlikely to be exposed to the notified chemical except in cases of drips and spills during charging or top up activities or during turbine maintenance work. Exposure to the notified chemical at concentrations of < 70% will primarily be dermal although ocular exposure is also possible from drips and splashes. Dermal and ocular exposure is expected to be minimised by the use of personal protective equipment (gloves, safety glasses and overalls). Inhalation exposure is unlikely as the mixture containing the notified chemical has a very low vapour pressure and is not heated during transfer, charging or topping up operations. During end use, the turbine oil containing the notified chemical will be retained within a high integrity lubrication system; therefore, accidental loss is expected to be negligible.

6.1.2. Public exposure
Public exposure to the notified chemical is expected to be negligible. The product containing the notified chemical will be imported, warehoused and then transported to commercial end users only. Exposure to the public will only occur in the event of a spill or industrial accident during the transport and storage of the turbine oil containing the notified chemical.

6.2. Human health effects assessment

The results from toxicological investigations conducted on analogues of the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Analogue	*Endpoint*	*Result and Assessment Conclusion*
1 & 2	Rat, acute oral	low toxicity, LD50 >5000 mg/kg bw
3	Rat, acute oral	low toxicity, LD50 > 2000 mg/kg bw
4	Rat, acute oral	low toxicity, LD50 > 2000 mg/kg bw
1 & 2	Rat, acute dermal toxicity	low toxicity, LD50 >2000 mg/kg bw
3	Rat, acute dermal toxicity	low toxicity, LD50 > 2000 mg/kg bw
4	Rat, acute dermal toxicity	low toxicity, LD50 > 2000 mg/kg bw
1 & 2	Rabbit, skin irritation	slightly irritating
3	Rabbit, skin irritation	slightly irritating
4	Rabbit, skin irritation	slightly irritating
1 & 2	Rabbit, eye irritation	slightly irritating
3	Rabbit, eye irritation	slightly irritating
4	Rabbit, eye irritation	slightly irritating
1 & 2	Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
3	Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
4	Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
1 & 2	Rat, repeat dose oral toxicity – 28 days	NOAEL 150 mg/kg bw/day
3	Rat, repeat dose oral toxicity – 28 days	NOAEL 1000 mg/kg bw/day
4	Rat, repeat dose oral toxicity – 28 days	NOAEL 1000 mg/kg bw/day
1 & 2	Genotoxicity - bacterial reverse mutation	non mutagenic
3	Genotoxicity - bacterial reverse mutation	non mutagenic

4	Genotoxicity - bacterial reverse mutation	non mutagenic
1 & 2	Genotoxicity – in vitro Chromosome aberration in human lymphocytes	non genotoxic
3	Genotoxicity – in vitro Chromosome aberration in human lymphocytes	non genotoxic
4	Genotoxicity – in vitro Chromosome aberration in human lymphocytes	non genotoxic

Toxicokinetics, metabolism and distribution.
Based on the molecular weight (majority > 500 Da) and the lipophilicity of the notified chemical (water solubility < 3.22×10^{-4} g/L; log Pow > 6.5) dermal absorption is expected to be low, with the transfer from the stratum corneum into the epidermis expected to be slow.

Acute toxicity.
Based on the studies conducted in rats all the tested analogues were considered to be of low acute toxicity *via* the oral and dermal routes. The notified chemical is therefore expected to be of similarly low acute toxicity via these routes. The acute inhalation hazard of the notified chemical or of the analogues has not been determined. However, given the low volatility of the notified chemical (vapour pressure of 5.4×10^{-12} kPa at 25°C) it is not expected to pose a significant inhalation hazard.

Irritation and Sensitisation.
Based on studies conducted in rabbits and guinea pigs the tested analogues were found to be slightly irritating to the skin and eyes, and there was no indication of skin sensitisation. The notified chemical is therefore expected to be only a slight skin and eye irritant and is not expected to be a skin sensitiser.

Repeated Dose Toxicity (sub acute, sub chronic, chronic).
The 28-day repeated-dose oral toxicity studies conducted on Analogue 3 and Analogue 4 established the No Observed Adverse Effect Level (NOAEL) at 1000 mg/kg bw/day as no adverse effects were observed at all doses tested.
In a 28-day repeated-dose oral toxicity study using a mixture containing 30-70% Analogue 1 and < 70% Analogue 2 treatment-related increases in the liver weights were observed for animals of either sex treated at 1000 mg/kg bw/day and for males treated at 500 mg/kg bw/day. There were no concomitant histopathological changes. While an increase in liver weights can be an adaptive response, in the absence of detectable hepatocyte enlargement or enzyme induction this is merely speculative, and so the increase in liver weights is considered a possible adverse effect. Treatment-related effects on the kidneys in all treated males were observed. These were considered to be characteristics of α2-microglobulin nephropathy, a male rat specific phenomenon, and were therefore considered to not be relevant for determining human hazard. The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study, based on changes in the liver at higher doses.

Mutagenicity.
The tested analogues were found to not be mutagenic using a bacterial reverse mutation test, and is were not clastogenic to human lymphocytes in vitro. The notified chemical is therefore not expected to be a mutagen or clastogen.

Observations on Human Exposure.
No adverse human health effects noted from use of the notified chemical.

Classification
Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
Based on the toxicity data provided for the analogues the notified chemical is expected to be a slight eye and skin irritant, and is not expected to be a skin sensitiser. The analogues are not acutely toxic via the oral or dermal routes, but treatment-related effects were seen during sub-chronic exposure with a mixture containing 30-70% Analogue 1 and < 70% Analogue 2.

Acute toxic potential

The potential for acute exposure is greatest during end use where the notified chemical will primarily be manually poured from containers into the turbines. Exposure is most likely to occur via a dermal route although ocular exposure to the notified chemical during topping up, charging and maintenance activities is also possible. As the notified chemical is expected to be slightly irritating to eyes and skin, the workers should avoid skin and eye contact with the product containing the notified chemical at a concentration of < 70%. The risk is acceptable on the basis that the notified chemical is not classified as hazardous and exposure will be low and further reduced by and good worker practises such as the use of PPE (gloves, safety eyewear and overalls).

Repeat-dose toxic potential
There is potential for dermal exposure to the notified chemical during charging, topping up and maintenance activities. Dermal exposure will be limited by the use of PPE such as safety eyewear, gloves and overalls when handling products containing the notified polymer.

Dermal exposure to the notified chemical during topping up, charging and maintenance activities can be estimated using the EASE model assuming reasonable worst case defaults and based on non-dispersive use with intermittent direct handling (European Commission, 2003). This gives an estimated daily exposure of 0.4 mg/kg bw/day for a 70 kg worker (assumed 100% dermal absorption). Based on the lowest NOAEL seen for the analogues (150 mg/kg bw/day for the mixture containing 30-70% Analogue 1 and < 70% Analogue 2) derived from a 28-day rat oral repeat dose study the margin of exposure (MOE) for the proposed use is 375. A MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Therefore, the risk of systemic effects using modelled worker data is acceptable for workers involved in topping up, charging and maintenance activities.

The risk of repeated exposure is therefore considered acceptable considering the estimated MOE and the toxilogical profile of the notified chemical.

6.3.2. Public health
The risk to the public from exposure to the notified chemical is expected to be negligible, given that it will only be used by industry and will not be in any products available to the public.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be manufactured, formulated and packaged into end-use containers overseas, and therefore, there will be no environmental release in Australia from this stage of the notified chemical's life-cycle.

RELEASE OF CHEMICAL FROM USE
The notified chemical will be imported formulated in 1 L end-use containers. Due to the nature of the formulated end-use product and its proposed use, environmental release is expected to be limited to residual within the imported containers and from accidental spills during transport and use. It is estimated, by the notifier, that these sources of release will account for less than 1% of the total import volume of the notified chemical.

RELEASE OF CHEMICAL FROM DISPOSAL
Used formulated product containing the notified chemical is expected to be disposed of by accredited waste management companies. It will most likely be recycled, incinerated or disposed of in landfill in accordance with local government regulations. Incinerated notified chemical is expected to thermally decompose to form various oxides of carbon and hydrogen.

In the landfill environment the notified chemical is expected to be immobile and associate strongly with the organic compartment based on its very low water solubility, and high P_{OW} and K_{OC}. Over time, the notified chemical is expected to degrade via biotic and abiotic processes to form predominantly simple organic compounds.

7.1.2 Environmental fate

Three ready biodegradability study reports were submitted for four analogue chemicals. These showed 28 d biodegradation ranging from 14 – 62%, and it was concluded that the notified chemical cannot be classified as ready biodegradable based on the data for the analogue chemicals. For the details of the environmental fate studies please refer to Appendix C.

While the notified chemical has the potential to bioaccumulate based on its low water solubility and high P_{OW}, its potential to biodegrade, although not sufficiently to be classified as ready biodegradable, combined with negligible aquatic exposure suggest that this will not occur.

7.1.3 Predicted Environmental Concentration (PEC)

As aquatic exposure is not expected at any stage of the notified chemical's life-cycle within Australia, it is not possible to predict its environmental concentration.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on analogues of the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Analogue	*Endpoint*	*Result*	*Assessment Conclusion*
1 & 2	Fish Toxicity	LC_{50} >100 mg/L WAF	Not harmful
3	Fish Toxicity	LLR_{50} >100 mg/L WSF	Not harmful
4	Fish Toxicity	LLR_{50} >100 mg/L WSF	Not harmful
1 & 2	Daphnia Toxicity	E_iLR_{50} >100 mg/L WAF	Not harmful
3	Daphnia Toxicity	E_iLR_{50} >100 mg/L WSF	Not harmful
4	Daphnia Toxicity	E_iLR_{50} >100 mg/L WSF	Not harmful
4	Daphnia Toxicity	E_iLR_{50} >1000 mg/L WSF	Not harmful
1 & 2	Algal Toxicity	E_rLR_{50} >100 mg/L WAF	Not harmful
3	Algal Toxicity	E_rLR_{50} >100 mg/L WSF	Not harmful
4	Algal Toxicity	E_rLR_{50} >100 mg/L WSF	Not harmful
1 & 2	Inhibition of Bacterial Respiration	E_iC_{50} >1000 mg/L	Not harmful
3	Inhibition of Bacterial Respiration	E_iC_{50} >1000 mg/L	Not harmful
4	Inhibition of Bacterial Respiration	E_iC_{50} >1000 mg/L	Not harmful

While ecotoxicity data were not provided for the notified chemical itself, thirteen studies were submitted for four analogues. No significant adverse effects were observed in any of the above tests, and it is concluded that the notified chemical is not expected to be harmful to aquatic life up to the level of its solubility in water.

7.2.1 Predicted No-Effect Concentration

As no significant adverse effects were observed in any of the ecotoxicity tests submitted, it is not appropriate to attempt to predict a no-effect concentration as this concentration would be significantly greater than the notified chemical's solubility in water.

7.3. Environmental risk assessment

Based on the lack of aquatic exposure, the potential to biodegrade and the absence of any observed adverse ecotoxicological effects, the proposed use of the notified chemical is not expected to pose an unacceptable risk to the environment.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

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

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

Environmental risk assessment
The notified chemical is not considered to pose a risk to the environment based on its proposed use pattern.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced in the product BP Turbo Oil 2380:
  - Avoid eye contact
  - Avoid skin contact

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced in the product BP Turbo Oil 2380:
  - Protective eyewear
  - Impervious gloves
  - Protective clothing

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)], workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of by recycling, incineration or to landfill.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the

notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

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

(1) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component (<70%) of aviation turbine oil, or is likely to change significantly;
- the amount of chemical being introduced has increased from 30 tonnes, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -20.2 ± 0.5ºC

Method OECD TG 102 Melting Point/Melting Range.
Remarks No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007a)

Boiling Point > 400 ± 0.5ºC at 99.97 kPa

Method OECD TG 103 Boiling Point.
ASTM E537-86
Remarks Determined using differential scanning calorimetry.
No significant protocol deviations. GLP compliant.
In addition the boiling point was calculated (using an adaptation of the Stein and Brown MPBP Win version 1.41) to be 504.85°C.
Test Facility Safepharm Laboratories (2007a)

Density 946 kg/m^3 at 20.4 ± 0.5ºC

Method OECD TG 109 Density of Liquids and Solids.
Remarks The relative density was determined using a pycnometer.
No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007a)

Vapour Pressure 5.4×10^{-12} kPa at 25°C

Method OECD TG 104 Vapour Pressure.
Remarks The vapour pressure was measured using a vapour pressure balance method.
No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007b)

Water Solubility $<3.22 \times 10^{-4}$ g/L at 20 ± 0.5°C

Method OECD TG 105 Water Solubility.
Remarks Flask Method. No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007a)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ (years)*
4	25	>1
7	25	>1
9	25	>1

Remarks No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007a)

Partition Coefficient (n-octanol/water) log P_{OW} = >6.50 at 20°C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method. The notified chemical eluted after the reference chemical "DDT". No significant protocol deviations. GLP compliant.
Test Facility Safepharm Laboratories (2007a)

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

Method	OECD TG 121 Adsorption HPLC Screening Method.
Remarks	HPLC Screening Method. The notified chemical eluted after the reference chemical "DDT". No significant protocol deviations. GLP compliant.
Test Facility	Safepharm Laboratories (2007a)

Flash Point 223 ± 2ºC at 101.3 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Closed cup, equilibrium method No significant protocol deviations. GLP compliant.
Test Facility	Safepharm Laboratories (2007b)

Autoignition Temperature 394 ± 5ºC

Method	EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	No significant protocol deviations. GLP compliant.
Test Facility	Safepharm Laboratories (2007b)

Explosive Properties Not explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Based on the chemical structure the notified chemical the result for the explosive properties test is predicted to be negative. No significant protocol deviations. GLP compliant.
Test Facility	Safepharm Laboratories (2007b)

Oxidizing Properties Not oxidising

Method	EC Directive 2004/73/EC A.21 Oxidizing Properties (Liquids).
Remarks	Based on the chemical structure the notified chemical the result for the oxidising properties test is predicted to be negative. No significant protocol deviations. GLP compliant.
Test Facility	Safepharm Laboratories (2007b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2
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 CD (Crl:CD BR)
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	5000	0/10

LD50	> 5000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted during the study. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths and no overt signs of systemic toxicity.
CONCLUSION	The mixture containing 30-70% Analogue 1 and < 70% Analogue 2 is of low toxicity via the oral route
TEST FACILITY	Safepharm Laboratories (1998a)

B.2. Acute toxicity – oral

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 92/69/EEC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD (Crl:CD (SD) IGS BR)
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 male	2000	0/3
2	3 female	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted during the study. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths and no overt signs of systemic toxicity.
CONCLUSION	Analogue 3 is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories (1999a)

B.3. Acute toxicity – oral

TEST SUBSTANCE	Analogue 4 – Test 1
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 92/69/EEC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD (Crl:CD BR)
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 male	2000	0/3
2	3 female	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted during the study. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths and no overt signs of systemic toxicity.

CONCLUSION	Analogue 4 is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories (1999b)

B.4. Acute toxicity – oral

TEST SUBSTANCE	Analogue 4 – Test 2
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 96/54/EEC B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD (Crl:CD (SD) IGS BR)
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 male	2000	0/3
2	3 female	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted during the study. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths and no overt signs of systemic toxicity.

CONCLUSION	Analogue 4 is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories (1999c)

B.5. Acute toxicity – dermal

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2
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 CD (Crl:CD BR)
Vehicle	Test substance administered as supplied
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of skin irritation.
Signs of Toxicity - Systemic	There were no signs of systemic toxicity. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths during the study.
CONCLUSION	The mixture containing 30-70% Analogue 1 and < 70% Analogue 2 is of low toxicity via the dermal route.
TEST FACILITY	Safepharm Laboratories (1998b)

B.6. Acute toxicity – dermal

TEST SUBSTANCE	Analogue 3
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 CD (Crl:CD BR)
Vehicle	Test substance administered as supplied
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of skin irritation.
Signs of Toxicity - Systemic	There were no signs of systemic toxicity. All animals showed an expected gain in bodyweight during the study.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	There were no deaths during the study.
CONCLUSION	Analogue 3 is of low toxicity via the dermal route.
TEST FACILITY	Safepharm Laboratories (1999d)

B.7. Acute toxicity – dermal

TEST SUBSTANCE	Analogue 4

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 CD (Crl:CD BR)
Vehicle Test substance administered as supplied
Type of dressing Semi-occlusive.
Remarks - Method No significant protocol deviations. GLP compliant.

RESULTS

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

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local There were no signs of skin irritation.
Signs of Toxicity - Systemic There were no signs of systemic toxicity. All animals showed an expected gain in bodyweight during the study.
Effects in Organs No abnormalities were noted at necroscopy.
Remarks - Results There were no deaths during the study.

CONCLUSION Analogue 4 is of low toxicity via the dermal route.

TEST FACILITY Safepharm Laboratories (1999e)

B.8. Irritation – skin

TEST SUBSTANCE Mixture containing 30-70% Analogue 1 and < 70% Analogue 2

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Vehicle Test substance administered as supplied
Observation Period 7 Days
Type of Dressing Semi-occlusive.
Remarks - Method No significant protocol deviations. GLP compliant.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.33	1.3	0.33	2	< 7 days	0
Oedema	0	0.33	0	1	< 48 hours	0

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

Remarks - Results Very slight erythema was noted at two treated skin sites at the 1 hour observation period. Very slight to well-defined erythema was noted at all treated skin sites at 24 hour observation. Very slight erythema was noted at one treated site at 48 and 72 hours.
Very slight oedema was noted at one treated skin site at 1 and 24 hour observation.
All treated skin sites appeared normal at 7 days.

CONCLUSION The mixture containing 30-70% Analogue 1 and < 70% Analogue 2 is slightly irritating to the skin.

TEST FACILITY Safepharm Laboratories (1998c)

B.9. Irritation – skin

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	Test substance administered as supplied
Observation Period	7 Days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP compliant.

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	1	1	0.7	1	< 7 days	0
Oedema	0	0	0	0		0

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

Remarks - Results	Very slight erythema was noted at all treated skin sites at the 24 and 48 hour observations and at two treated skin sites at the 72-hour observation. All treated skin sites appeared normal at the 7 day observation.
CONCLUSION	Analogue 3 is slightly irritating to the skin.
TEST FACILITY	Safepharm Laboratories (1999f)

B.10. Irritation – skin

TEST SUBSTANCE	Analogue 4
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	Test substance administered as supplied
Observation Period	7 Days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP compliant.

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	0.7	1	1	1	< 7 days	0
Oedema	0.3	1	0	1	< 7 days	0

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

Remarks - Results	Loss of skin elasticity was noted at one treated skin site at the 72-hour observation. Slight desquamation was noted at 2 treated skin sites on Day 7. Erythema and oedema was fully reversible at 7 days.
CONCLUSION	Analogue 4 is slightly irritating to the skin.

TEST FACILITY Safepharm Laboratories (1999g)

B.11. Irritation – eye

TEST SUBSTANCE Mixture containing 30-70% Analogue 1 and < 70% Analogue 2

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	3
Observation Period	72 hours
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

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

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

Remarks - Results
No corneal or iridal effects were noted during the study.
Moderate conjunctival irritation was note in all treated eyes at 1 hour.
All treated eyes appeared normal at the 24 hour observation.

CONCLUSION The mixture containing 30-70% Analogue 1 and < 70% Analogue 2 is slightly irritating to the eye.

TEST FACILITY Safepharm Laboratories (1998d)

B.12. Irritation – eye

TEST SUBSTANCE Analogue 3

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	3
Observation Period	72 hours
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0.3	0.3	2	< 48 hours	0
Conjunctiva: chemosis	0	0	0	1	< 24 hours	0
Conjunctiva: discharge	0	0	0.3	2	< 48 hours	0
Corneal opacity	0	0	0	0	0	0

Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results: Moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment, reducing after 24 hours to minimal conjunctival irritation for two animals and resolving completely for one animal. All effects had fully reversed in the other two animals by 48 hours after treatment. No corneal or iridial effects were noted.

CONCLUSION: Analogue 3 is slightly irritating to the eye.

TEST FACILITY: Safepharm Laboratories (1999h)

B.13. Irritation – eye

TEST SUBSTANCE: Analogue 4

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: 3
Observation Period: 72 hours
Remarks - Method: No significant protocol deviations. GLP compliant.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.7	0.3	0.3	2	< 72 hours	0
Conjunctiva: chemosis	0.7	0.3	0	2	< 72 hours	0
Conjunctiva: discharge	0.3	0.3	0	2	< 48 hours	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results: Moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment, reducing to minimal conjunctival irritation after 24 hours. All evidence of ocular irritation had fully reversed by 48 hours (2 animals) or 72 hours (1 animal) after treatment. No corneal or iridial effects were noted.

CONCLUSION: Analogue 4 is slightly irritating to the eye.

TEST FACILITY: Safepharm Laboratories (1999i)

B.14. Skin sensitisation

TEST SUBSTANCE: Mixture containing 30-70% Analogue 1 and < 70% Analogue 2

METHOD: OECD TG 406 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs.
EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs.

Species/Strain: Guinea pig/ Dunkin Hartley
PRELIMINARY STUDY: Maximum Non-irritating Concentration:
Intradermal: could not be determined, at 1% (lowest concentration tested) very slight to moderate/severe irritation was observed.

Topical: could not be determined, at 25% (lowest concentration tested) very slight irritation was observed.

MAIN STUDY

Number of Animals: Test Group: 20 Control Group: 10

INDUCTION PHASE

Induction Concentration:
Intradermal injection 25% w/v in arachis oil BP
topical application 100%

Signs of Irritation

Intradermal induction

Very slight or well defined erythema was noted at the intradermal induction site of all test group animals at 24 hours observation and 19 test animals at the 48 hour observation. Very slight erythema was noted at the intradermal induction sites of all control group animals at the 24 and 48 hour observation.

Topical induction

Very slight or well defined erythema and incidents of very slight oedema were noted at the induction sites of all test group animals at the 1 hour observation with very slight erythema and incidents of very slight oedema in ten test group animals at the 24 hour observation. Bleeding from the intradermal induction sites of four test group animals was noted at the 1 hour observation. Isolated incidents of small superficial scattered scabs or a hardened dark brown/black coloured scab were noted at 24 hour observation.

Bleeding from the intradermal induction sites were noted in one control animal at the 1 hour observation. No signs of erythema or oedema were noted at the treatment sites of control group animals at 1 and 24 hour observation.

CHALLENGE PHASE

1st challenge

intradermal: 100 %
topical: 75 %

Remarks - Method: No significant protocol deviations. GLP compliant.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	100 %	0	0
	75 %	0	0
Control Group	75 %	0	0
	100 %	0	0

Remarks - Results

No skin reactions were observed at the challenge sites of the control or test animals. Isolated incidents of small superficial scattered scabs or a hardened dark brown/black coloured scab were noted at the 24-hour observation.

Bodyweight gains of guinea pigs in the test group, between Day 0 and Day 24 were comparable to those observed in the control group animals over the same period.

CONCLUSION

There was no evidence of reactions indicative of skin sensitisation to the mixture containing 30-70% Analogue 1 and < 70% Analogue 2 under the conditions of the test.

TEST FACILITY

Safepharm Laboratories (1998e)

B.15. Skin sensitisation

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 406 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs. EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs.
Species/Strain	Guinea pig/Albino Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 25% topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 25% w/v in arachis oil BP topical: 100%
Signs of Irritation	*Intradermal induction* Very slight to well-defined erythema was noted at the intradermal induction sites of all test group animals at the 24 and 48 hour observations. Very slight erythema was noted at the intradermal induction sites of three control group animals at the 24 and hour observation and 2 control group animals at the 48 and hour observation. *Topical induction* Skin reactions observed after topical induction presented as very slight or well-defined erythema and an isolated incident of very slight oedema were noted at the induction sites of all test group animals at the 1-hour observation and five test group animals at the 24-hour observation. Bleeding from the intradermal induction sites was noted in three test group animals at the 1-hour observation. Residual test material was noted at the induction sites of three test group animals at the 1-hour observation. Very slight erythema was noted at the treatment site of one control group animal at the 1-hour observation. No evidence of skin irritation was noted at the treatment sites of control group animals at the 24-hour observation.
CHALLENGE PHASE	
1st challenge	topical: 100% topical: 75% v/v in arachis oil BP
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	100	0/10	0/10
	75	0/10	0/10
Control Group	100	0/5	0/5
	75	0/5	0/5

Remarks - Results	No skin reactions were noted at the challenge sites of either test or control group animals at the 24 or 48 hour observations. Body weight gain for the test group animals was comparable to that for the control group animals.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to analogue 3 under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1999j)

B.16. Skin sensitisation

TEST SUBSTANCE	Analogue 4
METHOD	OECD TG 406 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs. EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson and Kligman Maximisation Study in Guinea Pigs.
Species/Strain	Guinea pig/Albino Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 25% topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 25% w/v in arachis oil BP topical: 100%
Signs of Irritation	*Intradermal induction* Well-defined erythema was noted at the intradermal induction sites of all test group animals at the 24 and 48 hour observations. Very slight erythema was noted at the intradermal induction sites of all control group animals at the 24 and hour observation and 4 control group animals at the 48 and hour observation. *Topical induction* Skin reactions observed after topical induction presented as very slight or well-defined erythema and an isolated incident of very slight oedema were noted at the induction sites of 4 test group animals at the 1-hour observation. With very slight erythema and an isolated incident of very slight oedema at the 24 hour observation. Residual test material was noted at the induction site of 1 test group animal at the 1-hour observation. No evidence of skin irritation was noted at the treatment sites of control group animals at the 1 and 24-hour observations.
CHALLENGE PHASE	
1st challenge	topical: 100% topical: 75% v/v in arachis oil BP
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	100	0/10	0/10
	75	0/10	0/10
Control Group	100	0/4	0/4
	75	0/4	0/4

Remarks - Results	No skin reactions were noted at the challenge sites of either test or control group animals at the 24 or 48 hour observations. Body weight gain for the test group animals was comparable to that for the control group animals. One control group animal was killed on day 21 due to respiratory problems, this death did not affect the outcome of the study.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to analogue 4 under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1999k)

B.17. Repeat dose toxicity

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/ Sprague-Dawley Crl:CD BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

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

Mortality and Time to Death
There were no deaths during the study.

Clinical Observations
No clinical signs of toxicity were observed during the study.
One male treated at the high dose showed red/brown staining around the eye on Day 18 and 19 whilst one female showed red/brown staining around the ano-genital area from Day 18 onward. A second female showed red/brown staining around the ano-genital area from Day 22 to Day 27. These isolated, incidental external changes considered of no toxicological importance.

Functional observations
All the inter and intra group differences in urination, defecation and transfer arousal scores were considered to be a result of normal variation of rats of the strain and age used in the study and therefore are of no toxicological significance.

There were no treatment related changes in the functional performance parameter measured. Statistical analysis of the data revealed no intergroup differences.

Sensory reactivity assessment did not reveal any treatment related changes. All inter and intra group differences in sensory scores were considered to be the result of normal variation for rats of the strain and age used in the study therefore they are considered of no toxicological significance. Statistical analysis of the startle reflex data revealed no intergroup differences.

No adverse effect on bodyweight development was detected during the study. A statistically significant ($p< 0.01$) reduction weight was detected for 150 mg/kg bw/day females during the first week. However, in the absence of a dose response relationship, the slight intergroup difference was regarded as incidental and of no toxicological significance.

A slight reduction in food consumption was detected for females treated with 1000 mg/kg bw/day throughout the dosing period when compared with controls. Food efficiency (the ratio of bodyweight gain to dietary intake) however was similar to that of the controls for the same period. No adverse effect on dietary intake was observed for 1000 mg/kg bw/day males or animals of either sex treated at 500 or 150 mg/kg bw/day. Daily visual inspection of water bottles revealed no intergroup difference.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology
A statistically significant ($p< 0.05$) increase in haemoglobin was detected for 1000 mg/kg bw/day males when compared to the control animals but in the absence of any other changes in haematological correlates, this was considered of no toxicological significance.

A statistically significant ($p< 0.05$) increase in plasma inorganic phosphorous was detected for 1000 mg/kg bw/day males when compared to the control, however in isolation this minimal intergroup difference was not considered to be toxicological significant.

Effects in Organs
Animals of either sex treated with 1000 mg/kg bw/day showed a statistically significant increase in liver weight both absolute ($p< 0.05$) and relative ($p< 0.05$) when compared with controls. This effect extended to the 500 mg/kg bw/day but statistical significance ($p< 0.05$) was only achieved for male relative liver weights.

Kidney weights in the males only were elevated at 1000 and 500 mg/kg bw/day. The difference achieved statistical significance ($p<0.05$) at 1000 mg/kg bw/day. The intergroup difference at 500 mg/kg bw/day failed to achieve statistically significance. A statistically significant ($p< 0.05$) increase in the relative kidney weight was observed at 500 and 1000 mg/kg bw/day. No effects were observed at 150 mg/kg bw/day.

All males treated with 1000 mg/kg bw/day showed speckled kidneys at terminal kill whilst two females from this treatment group showed pallor of the liver. One female treated with 500 mg/kg bw/day showed a pale liver at necropsy.

The remaining macroscopic findings including reddened or dark areas of the lungs, hydronephrosis and isolated gastric changes, while showing no dose-related response, were consistent with normally expected low incidence findings in laboratory maintained rats and therefore were considered to be of no toxicological significance.

Histopathology
Treatment related kidney changes were observed. Globular accumulations of the eosinophilic material were observed in the renal proximal tubular epithelium of males treated at 1000, 500 and 150 mg/kg bw/day. The presence of globular accumulations of eosinophilic material in the tubular epithelium is consistent with appearance of hydrocarbon nephropathy which results form the excessive accumulation of α_2 microglobulin in renal proximal tubular epithelial cells. This is a well-documented effect, peculiar to the male rat, which occurs in response to treatment with certain hydrocarbons. Female rats and other species do not develop "hydrocarbon nephropathy" and for this reason, the effect is not indicative of a hazard to human health.

All the remaining morphological changes were those commonly observed in laboratory maintained rats at the age and strain employed and there were no difference in incidence or severity between control and treatment group that were considered to be toxicological significance.

Remarks – Results
Terminal studies revealed an increased group mean liver weight at a dose of 1000 and 500 mg/kg bw/day and macroscopic examination of the tissues revealed two 1000 mg/kg bw/day and one 500 mg/kg bw/day female showing pallor of the liver. There was no evidence of histopathological change so the reason for the increased weight is unknown. Elevated liver weights can be associated with adaptive changes following treatment with xenobiotics but in the absence of detectable hepatocyte enlargement or enzyme induction this is only speculative.

Male animals exhibited characteristics of α2-microglobulin nephropathy, a phenomenon known to occur only in adult male rats; as such, this finding is without any interspecies toxicological significance.

Based on the increased liver weights the NOEL for females was established as 500 mg/kg bw/day. As treatment-related effects were observed for all males a NOEL cannot be established for males. However, as the kidney effects are considered to be male rat specific, the NOAEL for males was established as 150 mg/kg bw/day, based on the increases in liver weights at the two higher doses.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study, based on changes in the liver at higher doses.

TEST FACILITY Safepharm Laboratories (1998f)

B.18. Repeat dose toxicity

TEST SUBSTANCE Analogue 3

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 BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

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

Mortality and Time to Death
There were no deaths during the study.

Clinical Observations
No toxicologically relevant effects on functional and behavioural parameters, bodyweight and bodyweight gain, food consumption and clinical biochemistry parameters were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
High dose group males had significantly reduced mean corpuscular haemoglobin concentration; however, in the absence of corresponding alterations in related parameters, this finding is likely incidental and without toxicological significance.

Effects in Organs
Absolute epididymides weights of high dose group males were significantly decreased, but not after normalisation to bodyweight. There were no gross pathological abnormalities.
Histopathological examination identified minimal to moderate accumulation of eosinophilic material within the renal proximal tubules of three high dose males, consistent with α2-microglobulin nephropathy.

Remarks – Results
On the basis of these observations, repeated administration of the notified chemical to Sprague-Dawley rats did not produce evidence of treatment-related adverse effects in female animals. Male animals exhibited characteristics of α2-microglobulin nephropathy, a phenomenon known to occur only in adult male rats; as such, this finding is without any interspecies toxicological significance. Consequently, the NOAEL for the notified chemical is 1000 mg/kg bw/day.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on this being the highest dose that was tested.

TEST FACILITY Safepharm Laboratories (2000a)

B.19. Repeat dose toxicity

TEST SUBSTANCE	Analogue 4
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 BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: none
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5/sex	0	0/10
low dose	5/sex	15	0/10
mid dose	5/sex	150	0/10
high dose	5/sex	1000	0/10

Mortality and Time to Death

There were no deaths during the study.

Clinical Observations

Incidents of increased salivation were detected around the time of dosing in 1000 mg/kg/day animals from Day 14. Sporadic instances of diuresis, wet fur and red/brown staining of the ano-genital region were observed during the last half of the study. No toxicologically relevant effects on functional and behavioural parameters, bodyweight and bodyweight gain, food consumption and haematological parameters were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

A statistically significant decrease in plasma albumin concentration and an increase in plasma creatinine concentration observed in high dose group males is unlikely indicative of renal or hepatic dysfunction in the absence of correlated biomarkers of hepatic injury, alterations in plasma electrolyte levels and histopathological findings.

Effects in Organs

High dose group males treated with 1000 mg/kg/day showed a statistically significant increase in kidney weight (14%), relative to terminal bodyweight, which is likely related to the accumulation of α2-microglobulin in the proximal tubules observed during histopathological examination. Females treated with 1000 mg/kg/day showed a statistically significant increase in relative liver weight (11%) when compared with controls. The significant increase in relative liver weight in high dose group females and hepatocytic hypertrophy observed histologically in high dose group animals of both sexes is an indication of adaptation to increased metabolic requirements and is not toxicologically significant.

Gross pathological examination identified speckled kidneys in high dose males. The histopathological evidence of accumulated eosinophilic material within the renal proximal tubules of high and mid dose males is consistent with α2-microglobulin nephropathy.

Animals of either sex treated with 150 or 15 mg/kg/day showed no treatment-related macroscopic abnormalities at necropsy.

Remarks – Results

On the basis of these observations, repeated administration of the notified chemical to Sprague-Dawley rats did not produce evidence of treatment-related adverse effects in female animals. Male animals exhibited characteristics of α2-microglobulin nephropathy, a phenomenon known to occur only in adult male rats; as such, this finding is without any interspecies toxicological significance. Consequently, the NOAEL for the notified chemical is 1000 mg/kg bw/day.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on this being the highest dose that was tested.

TEST FACILITY	Safepharm Laboratories (1999l)

B.20. Genotoxicity – bacteria

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA$^-$.
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 50 - 5000µg/plate. b) Without metabolic activation: 50 - 5000µg/plate.
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Remarks - Results	The test material caused no visible reduction in the growth of the bacterial lawn at any dose level. The test material was therefore tested up to the maximum recommended dose of 5000 µg/plate. An oily precipitate was observed at 5000 µg/plate, this did not prevent the testing of revertant colonies. No significant increases in frequency of revertant colonies were recorded for any of the bacterial strain, with any dose of the test material, with or without metabolic activation. The positive controls showed marked increases in the frequency of revertant colonies thus confirming the activity of the S9 mix and the sensitivity of the bacterial strains.
CONCLUSION	The Mixture containing 30-70% Analogue 1 and < 70% Analogue 2 was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1998g)

B.21. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA$^-$.
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 50 - 5000 µg/plate b) Without metabolic activation: 50 - 5000 µg/plate
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Remarks - Results	The test material caused no visible reduction in the growth of the bacterial lawn at any dose level. The test material was therefore tested up to the maximum recommended dose of 5000 µg/plate. An oily precipitate was observed at 5000 µg/plate, this did not prevent the testing of revertant colonies. No significant increases in frequency of revertant colonies were recorded for any of the bacterial strain, with any dose of the test material, with or without metabolic activation. The positive controls showed marked increases in the frequency of revertant colonies thus confirming the activity of the S9 mix and the sensitivity of the bacterial strains.
CONCLUSION	Analogue 3 was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1999m)

B.22. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 4 – Test 1
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA$^-$.
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 50 - 5000 µg/plate b) Without metabolic activation: 50 - 5000 µg/plate
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Remarks - Results	The test material caused no visible reduction in the growth of the bacterial lawn at any dose level. The test material was therefore tested up to the maximum recommended dose of 5000 µg/plate. An oily precipitate was observed at 5000 µg/plate, this did not prevent the testing of revertant colonies. No significant increases in frequency of revertant colonies were recorded for any of the bacterial strain, with any dose of the test material, with or without metabolic activation. The positive controls showed marked increases in the frequency of revertant colonies thus confirming the activity of the S9 mix and the sensitivity of the bacterial strains.
CONCLUSION	Analogue 4 was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1999n)

B.23. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 4 – Test 2
METHOD	OECD TG 471 Bacterial Reverse Mutation Test.

	EC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA$^-$.
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 50 - 5000 µg/plate b) Without metabolic activation: 50 - 5000 µg/plate
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Remarks - Results	The test material caused no visible reduction in the growth of the bacterial lawn at any dose level. The test material was therefore tested up to the maximum recommended dose of 5000 µg/plate. An oily precipitate was observed at 5000 µg/plate, this did not prevent the testing of revertant colonies. No significant increases in frequency of revertant colonies were recorded for any of the bacterial strain, with any dose of the test material, with or without metabolic activation. The positive controls showed marked increases in the frequency of revertant colonies thus confirming the activity of the S9 mix and the sensitivity of the bacterial strains.

CONCLUSION	Analogue 4 was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (1999o)

B.24. Genotoxicity – in vitro

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Cultured human peripheral lymphocytes
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction.
Vehicle	Acetone
Remarks - Method	In experiment 2, the final S9 concentration was increased from 1 to 2%. GLP compliant.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 39.06, 78.13, 156.25, 312.25, 625*, 1250*, 2500*, 5000*	4	20
Test 2	0*, 39, 78.1, 156.25, 312.5, 625*, 1250*, 2500*, 5000*	20	20
Present			
Test 1	0*, 39.06, 78.13, 156.25*, 312.5, 625*, 1250*, 2500*, 5000*	4	20
Test 2	0*, 156.25, 312.5, 625, 1250*, 2500*, 5000*	4	20

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	> 5000	≥ 625	Negative

Test 2		> 5000	≥ 2500	Negative
Present				
Test 1	> 5000	> 5000	≥ 625	Negative
Test 2		> 5000	≥ 1250	Negative

Remarks - Results

Experiment 1
The test substance induced statistically significant ($p \leq 0.05$) increases in the frequency of the cells with gap-type aberrations at 2500 and 5000 µg/mL in the absence of S9 and at 5000 µg/mL in the presence of S9.
The test material did not induce a significant increase in the numbers of polypoid cells at any dose level in either of the treatment cases.

Experiment 2
The test material did not induce any statistically significant increases in the frequency of cells with chromosome aberrations, either including or excluding gaps, in the presence of metabolic activation (at 2% concentration) or with continuous 20 hour exposure in the absence of S9. Therefore the small increases observed in Experiment 1 were confirmed to be of no toxicological significance.
The test material did not induce a significant increase in the numbers of polypoid cells at any dose level in either of the treatment cases.

CONCLUSION

The test substance was not clastogenic to cultured human peripheral lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Safepharm Laboratories (1998h)

B.25. Genotoxicity – in vitro

TEST SUBSTANCE

Analogue 3

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 92/69/EEC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Cultured human peripheral lymphocytes
Metabolic Activation System: Aroclor 1254 induced rat liver S9 fraction.
Vehicle: Acetone
Remarks - Method: In experiment 2, the final S9 concentration was increased from 1 to 2%. GLP compliant.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours
Test 2	0*, 156.3, 312.5, 625, 1250*, 2500*, 5000*	20 hours	20 hours
Present			
Test 1	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours
Test 2	0*, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

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

Test 1	> 5000	> 5000	> 5000	Negative
Test 2		> 5000	> 5000	Negative

Remarks - Results
All vehicle (solvent) controls gave frequencies of cells with aberrations within the range expected for normal human lymphocytes.
All positive control treatments gave statistically significant increases in the frequency of cells with aberrations indicating a satisfactory test performance and activity of the metabolising system.
The test material did not induce any statistically significant increases in the frequency of cells with aberrations in either of two separate experiments.
A second experiment was conducted consisting of 20 hours continuous exposure in the absence of S9 (concentration range 1250-5000 µg/plate and 4 hours exposure (20 hour harvest time) in the presence of S9 at a concentration of 1250-5000 µg/plate.

CONCLUSION
Analogue 3 was not clastogenic to cultured human peripheral lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY
Safepharm Laboratories (2000b)

B.26. Genotoxicity – in vitro

TEST SUBSTANCE
Analogue 4

METHOD
OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 92/69/EEC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain: Cultured human peripheral lymphocytes
Metabolic Activation System: Aroclor 1254 induced rat liver S9 fraction.
Vehicle: Acetone
Remarks - Method: In experiment 2, the final S9 concentration was increased from 1 to 2%.
GLP compliant.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours
Test 2	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	20 hours	20 hours
Present			
Test 1	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours
Test 2	0*, 39.1, 78.1, 156.3, 312.5, 625, 1250*, 2500*, 5000*	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

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

Remarks - Results
All vehicle (solvent) controls gave frequencies of cells with aberrations within the range expected for normal human lymphocytes.
All positive control treatments gave statistically significant increases in the

	frequency of cells with aberrations indicating a satisfactory test performance and activity of the metabolising system. The test material did not induce any statistically significant increases in the frequency of cells with aberrations in either of two separate experiments. A second experiment was conducted consisting of 20 hours continuous exposure in the absence of S9 (concentration range 1250-5000 µg/plate and 4 hours exposure (20 hour harvest time) in the presence of S9 at a concentration of 1250-5000 µg/plate.
CONCLUSION	Analogue 4 was not clastogenic to cultured human peripheral lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (2000c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and <70% Analogue 2.
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge from the aerated stage of a local domestic wastewater treatment plant (Derbyshire, UK).
Exposure Period	28 d
Auxiliary Solvent	Nil
Analytical Monitoring	TOC
Remarks - Method	No significant deviation in protocol.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
1	5	1	24
2	17	2	53
3	23	3	59
6	25	6	62
8	39	8	66
16	46	16	79
24	59	24	86
28	62	28	91
29*	64	29*	92

*Day 29 values corrected to include any carry over of CO_2 detected in Absorber 2.

Remarks - Results	The test substance attained 62% degradation after 28 days. However, despite attaining in excess of 50% the test substance failed to satisfy the 10 day window validation criterion by which 60% degradation must be attained within 10 days of the degradation exceeding 10% and therefore cannot be considered to be readily biodegradable under the strict terms of the test. All test validation criteria were satisfied.
CONCLUSION	The test substance cannot be classed as ready biodegradable.
TEST FACILITY	Safepharm Laboratories (1998i)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sewage sludge
Exposure Period	28 d
Auxiliary Solvent	Nil
Analytical Monitoring	CO_2 evolution
Remarks - Method	In order to aid dispersion of the low water solubility test material in the test system and to increase the surface area of test material available to the activated sewage sludge micro-organisms the test material was absorbed onto silica gel prior to addition to the test vessels. No significant protocol deviations.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	4	1	9
3	0	3	54
8	3	8	73
14	5	14	80
22	3	22	88
28	14	28	100
29*	21	29*	100

*Day 29 values corrected to include any carry over of CO_2 detected in Absorber 2.

Remarks - Results	The test substance attained 14% degradation after 28 days. All test validation criteria were satisfied.
CONCLUSION	The notified chemical cannot be classified as ready biodegradable.
TEST FACILITY	Safepharm Laboratories (2000d)

C.1.3. Ready biodegradability

TEST SUBSTANCE	Analogue 4
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sewage sludge
Exposure Period	28 d
Auxiliary Solvent	Nil
Analytical Monitoring	CO_2 evolution
Remarks - Method	In order to aid dispersion of the low water solubility test material in the test system and to increase the surface area of test material available to the activated sewage sludge micro-organisms the test material was absorbed onto silica gel prior to addition to the test vessels. No significant protocol deviations.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	3	1	9
3	1	1	54
8	24	24	73
14	33	14	80
22	33	22	88
28	39	28	100
29*	44	29*	100

*Day 29 values corrected to include any carry over of CO_2 detected in Absorber 2.

Remarks - Results	The test substance attained 39% degradation after 28 days. All test validation criteria were satisfied.
CONCLUSION	The notified chemical cannot be classified as ready biodegradable.
TEST FACILITY	Safepharm Laboratories (1999p)

C.1.4. Bioaccumulation

REMARKS	Not determined. The notified chemical has the potential to bioaccumulate

based on its physico-chemical properties. Although the analogous chemicals were not shown to be ready biodegradable, biodegradation between 14 – 62% occurred within the 28 day test period. Therefore, it is unlikely that the notified chemical will bioaccumulate. The potential for bioaccumulation is further minimised due to the expected negligible aquatic exposure of the notified chemical under its proposed use pattern within Australia.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and <70% Analogue 2.
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-static
Species	*Oncorhynchus mykiss*
Exposure Period	96 h
Auxiliary Solvent	Nil
Water Hardness	109 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test substance was prepared as a Water Accommodated Fraction (WAF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	10	0	0	0	0	0
100	0.53	10	0	0	0	0	0

LC_{50}	>100 mg/L (WAF) at 96 hours.
NOEC	100 mg/L (WAF) at 96 hours.
Remarks – Results	The results based on the TWA mean measured test concentration gave a 96 hour Lethal Loading Rate (LLR) >0.53 mg/L.
CONCLUSION	Under the study conditions the test substance is not harmful to rainbow trout up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1998j)

C.2.2. Acute toxicity to fish

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-static
Species	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	Nil
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*

Nominal	*Actual*		*3 h*	*6 h*	*24h*	*48h*	*72h*	*96h*
0	0	10	0	0	0	0	0	0
100	<0.00613	10	0	0	0	0	0	0

LLR_{50}	>100 mg/L nominal loading rate WSF at 96 hours.
NOELR	100 mg/L nominal loading rate WSF at 96 hours.
Remarks – Results	No effects were observed. Analysis of the 100 mg/L loading rate WSF showed the measured test concentration to be below the limit of quantification (0.00613 mg/L) of the analytical method employed.

CONCLUSION Under the study conditions the test substance is not harmful to rainbow trout up to the limit of its water solubility.

TEST FACILITY Safepharm, Derby, U.K. (2000e)

C.2.3. Acute toxicity to fish

TEST SUBSTANCE Analogue 4

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi-static
EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-static

Species	*Oncorhynchus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	Nil
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*					
Nominal	*Actual*		*3 h*	*6 h*	*24h*	*48h*	*72h*	*96h*
0	0	10	0	0	0	0	0	0
100	<0.02	10	0	0	0	0	0	0

LLR_{50}	> 100 mg/L nominal loading rate WSF at 96 hours.
NOELR	100 mg/L nominal loading rate WSF at 96 hours.
Remarks – Results	No effects were observed. Analysis of the 100 mg/L loading rate WSF showed the measured test concentration to be below the limit of quantification (0.02 mg/L) of the analytical method employed.

CONCLUSION Under the study conditions the test substance is not harmful to rainbow trout up to the limit of its water solubility.

TEST FACILITY Safepharm, Derby, U.K. (1999q)

C.2.4. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Mixture containing 30-70% Analogue 1 and < 70% Analogue 2.

METHOD OECD TG 202 *Daphnia sp.* Acute Immobilisation Test and Reproduction Test - Static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Nil
Water Hardness	116 mg $CaCO_3$/L

Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Accommodated Fraction (WAF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
100	0.40	40	0	0

E_iLR_{50}	>100 mg/L (WAF) at 48 hours
NOE_iLR	100 mg/L (WAF) at 48 hours
Remarks - Results	No effects were observed. The 48-Hour E_iLR_{50}, based on the time-weighted mean measured concentrations, was greater than 0.40 mg/L and correspondingly the NOE_iLR was equal to 0.40 mg/L.

CONCLUSION	Under the study conditions the test substance is not harmful to Daphnids up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1998k)

C.2.5. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - <insert test type/conditions>. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - <insert test type/conditions>.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Nil
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
100	0.00613	40	0	0

E_iLR50	>100 mg/L (WSF) at 48 hours
NOE_iLR	100 mg/L (WSF) at 48 hours
Remarks - Results	No effects were observed. Analysis of the 100 mg/L loading rate WSF showed the measured test concentration to be below the limit of quantification (0.00613 mg/L) of the analytical method employed.
CONCLUSION	Under the study conditions the test substance is not harmful to Daphnids up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (2000f)

C.2.6. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue 4 – Test 1
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Nil
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
100	0.02	40	0	0

E_ILR50	>100 mg/L nominal loading rate WSF at 48 hours.
NOE_ILR	100 mg/L nominal loading rate WSF at 48 hours.
Remarks - Results	No effects were observed. Analysis of the 100 mg/L loading rate WSF showed the measured test concentration to be below the limit of quantification (0.02 mg/L) of the analytical method employed.
CONCLUSION	Under the study conditions the test substance is not harmful to Daphnids up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1999r)

C.2.7. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue 4 – Test 2
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Nil
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Accommodated Fraction (WAF) due to its low water solubility. No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
1000	0.032	40	0	0

E_ILR50	>1000 mg/L nominal loading rate WAF at 48 hours.
NOE_ILR	1000 mg/L nominal loading rate WAF at 48 hours.
Remarks - Results	No effects were observed. Analysis of the 1000 mg/L loading rate WAF showed the measured test concentration to be below the limit of quantification (0.032 mg/L) of the analytical method employed.

CONCLUSION	Under the study conditions the test substance is not harmful to Daphnids up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (2003a)

C.2.8. Algal growth inhibition test

TEST SUBSTANCE	Mixture containing 30-70% Analogue 1 and < 70% Analogue 2.
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours
Concentration Range	Nominal: 100 mg/L Actual: < LOQ (= 0.73 mg/L)
Auxiliary Solvent	Nil
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Accommodated Fraction (WAF) due to its low water solubility. No significant protocol deviations.

RESULTS

Biomass		*Growth*	
E_bLR_{50} *mg/L at 96 h*	NOE_bLR *mg/L*	E_rLR_{50} *mg/L at 0 – 96 h*	NOE_rLR *mg/L*
>100 (WAF)	100 (WAF)	> 100 (WAF)	100 (WAF)

Remarks - Results	No effects were observed. Analysis of the 100 mg/L loading rate WAF showed the measured test concentration to be below the limit of quantification (0.73 mg/L) of the analytical method employed.
CONCLUSION	Under the study conditions the test substance is not harmful to alga up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1998l)

C.2.9. Algal growth inhibition test

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: <LOQ (= 0.18 mg/L)
Auxiliary Solvent	Nil
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Biomass		*Growth*	
E_bLR_{50} *mg/L at 72 h*	NOE_bLR *mg/L*	E_rLR_{50} *mg/L at 0 – 72 h*	NOE_rLR *mg/L*
>100 (WSF)	100 (WSF)	>100 (WSF)	100 (WSF)

Remarks - Results	No effects were observed. Analysis of the 100 mg/L loading rate WSF

showed the measured test concentration to be below the limit of quantification (0.18 mg/L) of the analytical method employed.

CONCLUSION Under the study conditions the test substance is not harmful to alga up to the limit of its water solubility.

TEST FACILITY Safepharm Laboratories (2000g)

C.2.10. Algal growth inhibition test

TEST SUBSTANCE Analogue 4

METHOD OECD TG 201 Alga, Growth Inhibition Test.
EC Directive 92/69/EEC C.3 Algal Inhibition Test.

Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: 2 – 6% of Nominal
Auxiliary Solvent	Nil
Analytical Monitoring	GC
Remarks - Method	The test substance was prepared as a Water Soluble Fraction (WSF) due to its low water solubility. No significant protocol deviations.

RESULTS

Biomass		*Growth*	
E_bLR_{50} *mg/L at 72 h*	NOE_bLR *mg/L*	E_rLR_{50} *mg/L at 0 – 72 h*	NOE_rLR *mg/L*
>100 (WSF)	100 (WSF)	> 100 (WSF)	100 (WSF)

Remarks - Results No effects were observed. Analysis of the 100 mg/L loading rate WSF showed the measured test concentration to be 2 – 6% of the nominal concentration after 72 h.

CONCLUSION Under the study conditions the test substance is not harmful to alga up to the limit of its water solubility.

TEST FACILITY Safepharm Laboratories (1999s)

C.2.11. Inhibition of microbial activity

TEST SUBSTANCE Mixture containing 30-70% Analogue 1 and < 70% Analogue 2.

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum	Activated sludge from the aerated stage of a local domestic wastewater treatment plant (Derbyshire, UK).
Exposure Period	3 hours
Concentration Range	Nominal: 1000 mg/L
Remarks – Method	No significant protocol deviations.

RESULTS

E_iC50	> 1000 mg/L
NOE_iC	1000 mg/L
Remarks – Results	A relatively large increase in respiration rats observed in the test vessels after 30 minutes contact time is considered to be due to the possible horrmetric response of activated sewage sludge micro-organisms to the

	test material.
CONCLUSION	Under the study conditions the test substance is not harmful to microbes up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1998m)

C.2.12. Inhibition of microbial activity

TEST SUBSTANCE	Analogue 3
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
INOCULUM	Activated sludge from the aerated stage of a local domestic wastewater treatment plant (Derbyshire, UK).
EXPOSURE PERIOD	3 hours
CONCENTRATION RANGE	Nominal: 1000 mg/L
REMARKS – METHOD	No significant protocol deviations.
RESULTS	
E_iC50	> 1000 mg/L
NOE_iC	1000 mg/L
Remarks – Results	No significant effect on respiration was observed at the test concentration employed.
CONCLUSION	Under the study conditions the test substance is not harmful to microbes up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1999t)

C.2.13. Inhibition of microbial activity

TEST SUBSTANCE	Analogue 4
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
INOCULUM	Activated sludge from the aerated stage of a local domestic wastewater treatment plant (Derbyshire, UK).
EXPOSURE PERIOD	3 hours
CONCENTRATION RANGE	Nominal: 1000 mg/L
REMARKS – METHOD	No significant protocol deviations.
RESULTS	
E_iC50	> 1000 mg/L
NOE_iC	1000 mg/L
Remarks – Results	No significant effect on respiration was observed at the test concentration employed.
CONCLUSION	Under the study conditions the test substance is not harmful to microbes up to the limit of its water solubility.
TEST FACILITY	Safepharm Laboratories (1999u)

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