File No: STD/1428

January 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1,6-Hexanediamine, N1,N6-bis(1,2,2-trimethylpropyl)-

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 Sustainability, Environment, Water, Population and Communities.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This 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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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1428	Albemarle Singapore Pty Ltd	1,6-Hexanediamine, N1,N6-bis(1,2,2-trimethylpropyl)-	Yes	≤100 tonnes per annum	Component of coatings

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the Table below.

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage
Skin sensitisation (Category 1)	H317 – May cause an allergic reaction
Specific Target Organ Toxicity - Repeated Exposure (Category 1)	H372 – Causes damage to organs

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

R22	Harmful if swallowed
R38	Irritating to skin
R41	Risk of serious eye damage
R43	May cause sensitisation by skin contact
R48/22	Harmful: Danger of serious damage to health by prolonged exposure if swallowed

The environmental hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute (Category 1)	Very toxic to aquatic life
Chronic (Category 1)	Very toxic to aquatic life with long lasting effects

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

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

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

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - H302 – Harmful if swallowed
  - H318 – Causes serious eye damage
  - H317 – May cause an allergic reaction
  - H372 – Causes damage to organs

- The following classifications should be considered for use for products/mixtures containing the notified chemical:
  - Conc. ≥25%: H302, H318, H317, H372
  - 25% >Conc. ≥10%: H318, H317, H372
  - 10% >Conc. ≥3%: H318, H317, H373*
  - 3% >Conc. ≥1%: H317, H373

  *H373 – May cause damage to organs

- The notifier should consider their obligations under the Australian Dangerous Goods Code.

Health Surveillance

- As the notified chemical has skin sensitisation potential, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

CONTROL MEASURES
Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Automated and enclosed processes for mixing and coating, where possible

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Eye and face protection
  - Appropriately fitted respiratory protection during spray application
  - Impervious coveralls
  - Impervious gloves
  - Impervious footwear

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

- Spray applications should be carried out in accordance with the Safe Work Australia *National Guidance Material for Spray Painting* (NOHSC, 1999) or relevant State and Territory Codes of Practice.

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

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

Disposal

- The notified chemical should be disposed of 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 of coatings, or is likely to change significantly;
- the amount of chemical being introduced has increased from 100 tonnes per annum, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Albemarle Singapore Pty Ltd (ABN: 30 061 231 229)
Level 10, 68 Pitt Street
Sydney NSW 2000

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: import volume and identity of recipients.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA, Korea

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Ethacure® 90

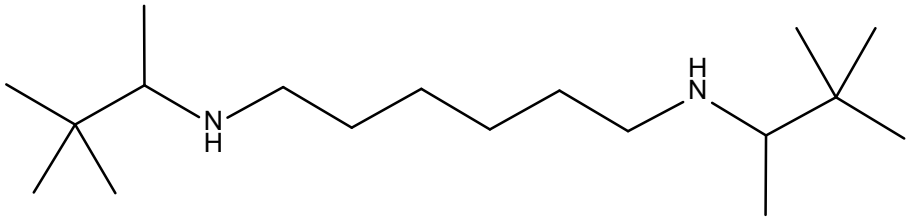
CAS NUMBER
957787-76-7

CHEMICAL NAME
1,6-Hexanediamine, N1,N6-bis(1,2,2-trimethylpropyl)-

OTHER NAME(S)
SD-10

MOLECULAR FORMULA
$C_{18}H_{40}N_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
284.5 Da

ANALYTICAL DATA
Reference NMR and GC-MS spectra were provided.

3. COMPOSITION

DEGREE OF PURITY ≥94%

IDENTIFIED IMPURITIES

Chemical Name 1,6-Hexanediamine, N1,N6-bis(1,2,2-trimethylpropyl)-
CAS No. 74912-32-6 *Weight %* 2

Chemical Name 1,6-Hexanediamine, N-(1,2,2-trimethylpropylidene)-, N'-(1,2,2-trimethylpropyl)-
CAS No. Not assigned *Weight %* 2

Chemical Name 1,6-Hexanediamine, N1-bis(1,2,2-trimethylpropyl)-, N'-(other substituted butyl groups)-
CAS No. Not assigned *Weight %* 2

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	<-20 °C	Measured
Boiling Point	321 ± 1 °C at 100.6 kPa	Measured

Density	830 kg/m^3 at 20 °C	Measured
Vapour Pressure	5.9 x 10^{-5} kPa at 25 °C	Measured
Water Solubility	8.64 x 10^{-2} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ > 1 year at 25 ºC (pH 4, 7, 9)	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.10 at 22 °C	Measured
Surface Tension	59.6 mN/m at 22.6 °C	Measured
Adsorption/Desorption	Estimated log K_{oc} = 4.46 and 1.99	Calculated using KOCWIN (v2.00) with MCI and Pow methods, respectively, based on the measured log Pow (US EPA, 2012)
Dissociation Constant	Estimated pKa = 10.91 and 11.56	Calculated. Expected to be ionised under environmental conditions
Flash Point	147 ± 2 °C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be flammable based on flash point
Autoignition Temperature	248 ± 5 °C	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would infer explosive properties
Oxidising Properties	Predicted negative	Contains no functional groups that would infer oxidising properties

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

Reactivity
The notified chemical is stable under normal conditions of use and hazardous reactions should not occur. However, reactions with oxidising materials are expected and contact with oxidising materials should be avoided.

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported at ≥94% concentration.

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

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

PORT OF ENTRY
Sydney and Melbourne.

TRANSPORTATION AND PACKAGING
The notified chemical (≥94% concentration) will be imported in 205 L drums or 800 kg totes. Formulated products will be contained in 5 or 20 L steel cans or in 205 L drums. The notified chemical will be transported within Australia by road.

USE
The notified chemical will be used as a component (5-20% concentration) of coatings for the lining of truck beds, ship hulls, secondary containment structures and the external and internal side of pipes (not intended for potable water sources).

OPERATION DESCRIPTION
Reformulation

The notified chemical (≥94% concentration) will be formulated into a component (containing 10-40% notified chemical) of a two part coating system. Reformulation will be mostly an automated process. The notified chemical (≥94% concentration) will be transferred from the drum or tote by hose into a closed mixing vessel. Samples will then be taken for quality control purposes. Filling containers with the final product (containing 10-40% notified chemical) will be an automated process.

Coating application
The formulated product (containing 10-40% notified chemical) will be combined with an equal amount of the second component. The mixed coating (5-20% notified chemical) will then be applied to the various substrates by brush, roller or spray. The two components will either be mixed inside the spray equipment or will be stirred by hand for brush or roller application.

Truck beds will be coated manually by workers within spray booths supplied with exhaust ventilation to collect overspray. Ship hulls will be coated by spray equipment (typically airless spray) whilst in dry dock using protective curtains and floor sheeting to collect overspray. Secondary containment structures will be coated in open air situations *in situ* by brush, roller or spray. Pipes will be coated in factories or at the use location, using automated spray equipment within continuous line spray booths.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Formulation	4	60
Warehouse	4	60
Disposal	4	60
Spray	8	60

EXPOSURE DETAILS
Occupational exposure to dock workers or during storage and transport is unlikely because the notified chemical will be packaged inside sealed containers. Exposure will only occur in the unlikely event of an accidental spill during transport or storage.

Reformulation
Dermal and ocular exposure of workers to the notified chemical may occur when reformulating the notified chemical as imported (≥94% concentration) into the end-use coating product (containing 10-40% notified chemical). Based on the high boiling point (321°C) and the low vapour pressure (5.9×10^{-5} kPa), inhalation exposure to the notified chemical is likely to be low during reformulation, except in the unlikely case of aerosol formation. Exposure will be minimised by the use of automated processes, local exhaust ventilation and PPE (industrial protective clothing, solvent resistant gloves, goggles and respirator).

Coating application
There is potential inhalation, dermal and ocular exposure of workers to the notified chemical when spraying truck beds, ship hulls, pipes and secondary containment structures. Depending on the substrate to which it is applied, measures to lower the exposure include the use of spray booths, automated spray equipment, and enclosed processes. Spraying workers are also expected to wear full face air supplied respirators, chemical goggles or face shield, disposable full-body protective overalls, safety boots and impermeable gloves, acting to lower exposure.

Dermal and ocular exposure may occur when mixing and applying the coating by brush or roller. Workers are expected to wear goggles or a face shield, disposable full-body protective overalls, safety boots and impermeable gloves. Although inhalation exposure is expected to be low, a respirator will be worn when there is inadequate ventilation.

6.1.2. Public Exposure

The coating component (containing 10-40% notified chemical) will not be available to the general public. Although unlikely, the public may be exposed to cured coatings (containing 5-20% notified chemical). However, once cured, the notified chemical will be trapped in an inert polymer matrix and unavailable for exposure.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following Table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 = 550 mg/kg bw; harmful
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw; low toxicity
Rabbit, skin irritation	irritating
In vitro, skin irritation	non irritating
In vitro, skin corrosion	non corrosive
In vitro, eye irritation	irritating
In vitro, eye corrosion	severe irritant to corrosive
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	LOAEL = 5 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* gene mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration	non clastogenic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non genotoxic

Toxicokinetics, metabolism and distribution.
No toxicokinetic data on the notified chemical were submitted. Absorption across the skin, gastrointestinal tract and respiratory tract is expected based on the low molecular weight (<500 Da), partition coefficient (Log Pow = 2.10) and water solubility (0.0864 g/L). This is supported by evidence of systemic toxicity observed in the acute oral toxicity and the 28-day repeat dose oral toxicity studies in rats.

Acute toxicity.
The notified chemical was harmful by the oral route (LD50 = 550 mg/kg bw) in rats. Mortalities (3/10) were also observed in rats in an *in vivo* micronucleus study with animals administered a single gavage dose of the notified chemical at 600 mg/kg bw. The notified chemical was of low acute dermal toxicity (LD50 >2000 mg/kg bw) in rats. There is no data available on the acute inhalation toxicity of the notified chemical.

Skin and eye irritation
Slightly irritating to irritating effects were seen in a skin irritation study in rabbits. The notified chemical was considered to be non-corrosive and non-irritating on the basis of two *in vitro* studies. However, based on the irritant effects observed *in vivo*, the notified chemical should be considered as a potential skin irritant.

The notified chemical was severely irritating to corrosive to the eyes in an *in vitro* study. Another *in vitro* study demonstrated that the notified chemical is an eye irritant. Based on these studies, the notified chemical is considered to be severely irritating to corrosive to eyes.

Skin sensitisation
The notified chemical is a skin sensitiser based on a positive result from an LLNA study in mice.

Repeated dose toxicity
In a 28-day repeat dose gavage study, rats were administered the notified chemical at 0, 5, 10 or 20 mg/kg bw/day, with additional groups maintained for a 14-day recovery period. There was some indication of an effect on body weight gain at 20 mg/kg bw/day but recovery was observed following cessation of treatment. Histopathological changes were observed in the heart, lung, liver, kidney, adrenals, thyroids, and the mesenteric and cervical lymph nodes. The relevance of necrotic effects observed in the heart of males at 20 mg/kg bw/day remains unclear, despite the apparent reversibility, as functional implications were not investigated in this study. Foamy macrophages were observed in the lungs in all female treatment groups and full reversibility was not observed. A NOAEL was therefore not established. The LOAEL was 5 mg/kg bw/day.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation assay or in an *in vitro* gene mutation assay and was not clastogenic in an *in vitro* chromosome aberration assay. These results were confirmed by a negative finding in an *in vivo* micronucleus study.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following Table.

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage
Skin sensitisation (Category 1)	H317 – May cause an allergic reaction
Specific Target Organ Toxicity Repeated Exposure (Category 1)	H372 – Causes damage to organs

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases:

R22	Harmful if swallowed
R38	Irritating to skin
R41	Risk of serious eye damage
R43	May cause sensitisation by skin contact
R48/22	Harmful: Danger of serious damage to health by prolonged exposure if swallowed

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical will be present at ≥94% concentration as imported or at 10-40% in the end-use formulation; therefore the toxicological effects of concern for workers are skin irritation, serious eye damage, skin sensitisation and systemic toxicity.

Dermal, ocular and possibly inhalation exposure of workers to the notified chemical may occur during reformulation processes. Exposure will be minimised by the use of automated processes, local exhaust ventilation and PPE (industrial protective clothing, solvent resistant gloves, goggles and respirator).

Dermal, ocular and inhalation exposure may occur during application of coatings. Exposure will be lowered by the use of engineering controls, automated equipment, and enclosed processes. In addition, workers are expected to wear PPE, which will include full face supplied air respirators during spray operations, and skin and eye protection during all application processes.

Overall, provided engineering controls are instituted, workers wear the PPE described above, and safe work practices are maintained to reduce exposure, the risk to workers is not considered to be unreasonable.

6.3.2. Public Health
Public exposure through dermal contact with cured coatings will be low because the notified chemical will be trapped in a polymer matrix and will be unavailable for exposure. The risk to public health is not considered unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be reformulated in Australia for use in coating products. The release of the notified chemical to the environment is likely due to accidental spills, leaks and washings from equipment cleaning during reformulation processes. These wastes (containing less than 0.6% of total annual import volume of the notified chemical) are expected to be collected with inert adsorbent material (sand, vermiculite, etc) and be disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

It is expected that the transfer of the coating to the substrate by roller or brush is very efficient. Therefore, the majority release of the notified chemical will be overspray during coating application by spray. It is estimated that up to 35% of the notified chemical will be released as overspray either within a spray booth or in other engineering devices. In spray booths, the overspray is expected to be collected using filters and water scrubbers. The filters will be disposed of to landfill. The notified chemical in the scrubber water will be removed as the inert solid after curing and be disposed of to landfill. When spraying is undertaken in outdoor areas, the overspray is expected to be collected on protective sheeting, cured and disposed as domestic waste to landfill.

Wastes from accidental spills (up to 0.2% of total annual import volume) and washings for application equipment (approximately 1%) are expected to be contained, collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

The majority of the notified chemical will be cured into an inert matrix with other chemical substances, as part of the coating process, and hence will be immobilised within a chemical film on coated articles. The chemical incorporated in the coating will be disposed of along with the coated articles and will either go to metal recyclers or be disposed of to landfill. Residues of the notified chemical in empty containers will be disposed of to landfill along with the containers.

7.1.2. Environmental Fate

The notified chemical will be used as a component of coatings for the lining of truck beds, ship hulls, secondary containment structures and the external and internal side of pipes. The notified chemical is expected to be cured into a solid matrix as part of its normal use pattern and is therefore not expected to be mobile, bioavailable or bioaccumulative in cured form. The majority of the notified chemical is expected to be ultimately disposed of to landfill or thermally decomposed during recycling of metal to which it is applied. The notified chemical is expected to be thermally degraded to gases of water and oxides of carbon and nitrogen during the metal recycling processes. The notified chemical is hydrolytically stable under environmental conditions and is not readily biodegradable. It is expected to eventually degrade by biotic and abiotic processes to form landfill gases of methane, water, oxides of carbon and nitrogen. For the details of the environmental fate studies please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

The notified chemical is not expected to be present in the aquatic environment because of the very low potential for release to surface waters when used in surface coatings. A predicted environmental concentration (PEC) has therefore not been calculated.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h) > 100 mg test substance/L WAF with 10 and 20 mg/L humic acid	Not harmful to fish *
Daphnia Toxicity	LC50 (48 h) = 0.4 % WAF of 100 mg test substance/L	Very toxic to aquatic invertebrates**
Algal Toxicity	E_rC50 (96 h) > 10 mg/L NOE_rC = 0.032 mg/L	Harmful to algae Very toxic to algae with long lasting effects
Inhibition of Bacterial Respiration	IC50 (3 h) = 500 mg/L	Not inhibitory to microorganism respiration

* Based on the tests done in the media with typical levels of total organic carbon in environment waters.
** The results are reported as a percentage of stock water accommodation fractions (WAF) rather than mg/L as the actual concentration of the notified chemical in the test solutions were not determined for daphnia toxicity study. As the water solubility of the notified chemical is less than 100 mg/L of the reported stock WAF concentration, the actual concentration of the notified chemical in the test solutions is expected to be equal to or less than % WAF × 100 mg test substance/L.

The notified chemical is not harmful to fish based on the test results conducted in media with typical levels of total organic carbon as in environmental waters. The toxicity endpoint for *daphnia* was derived from water accommodation fractions (WAF) test solutions that were prepared by serial dilution of a single stock WAF. It is considered to be indicative of unmitigated toxicity for the purpose of GHS classification. Therefore, based on the acute toxicity endpoint for *daphnia*, the notified chemical is formally classified as "Acute Category 1: Very toxic to aquatic life" under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009). The long-term classification for the notified chemical was determined based on the chronic toxicity endpoint for algae, noting that the notified chemical is not readily biodegradable. The notified chemical is formally classified under GHS as "Chronic Category 1: "Very toxic to aquatic life with long lasting effects".

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) was not calculated as no PEC was calculated.

7.3. Environmental Risk Assessment

A Risk Quotient (Q = PEC/PNEC) was not calculated as a PEC and PNEC were not determined. The reported use pattern of the notified chemical indicates that there is no significant anticipated aquatic release. After curing, the majority of the imported quantity of notified chemical will be incorporated into an inert matrix and is not expected to be mobile, bioavailable or bioaccumulative in this form. Although the notified chemical is very toxic to aquatic life, it is unlikely to pose a risk to the aquatic environment given that the environmental exposure is expected to be very limited. On the basis of the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point <-20°C

Method EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks 15 mL sample of the notified chemical was cooled to -21 °C whilst being continuously stirred. Freezing was not achieved but slightly increased viscosity was observed during cooling.
Test Facility Harlan (2011a)

Boiling Point 321 ± 1 °C at 100.59 kPa

Method EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks Determined using differential scanning calorimetry.
Test Facility Harlan (2011a)

Density 830 kg/m^3 at 20.0 °C

Method EC Council Regulation No 440/2008 A.3 Relative Density
Remarks Determined using a pycnometer.
Test Facility Harlan (2011a)

Vapour Pressure 5.9 x 10^{-5} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
Remarks Determined using vapour pressure balance.
Test Facility Harlan (2011b)

Water Solubility 8.64 x 10^{-2} g/L at 20 ± 0.5 °C

Method EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks Flask Method. Following the preliminary tests, triplicate test samples were prepared and test substance concentrations were analysed by gas chromatography (GC). The test solution pH was 10.2.
It is noted that any formation of a dispersion, emulsion or oily layer was not reported.
Test Facility Harlan (2010a)

Hydrolysis as a Function of pH $t_{½}$ > 1 year at pH 4, 7 and 9 at 25 °C

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 Preliminary tests were performed at 50 °C for pH 4, 7 and 9. At each pH value, less than 10% hydrolysis was observed after 5 days. This is equivalent to a half-life of > 1 year at 25 °C.
Test Facility Harlan (2011c)

Partition Coefficient (n-octanol/water) log Pow = 2.10 at 22 ± 0.5 °C

Method EC Council Regulation No 440/2008 A.8 Partition Coefficient
Remarks Shake flask method. Partition coefficient tests were conducted for the notified chemical at pH 9 with the notified chemical in its ionised form. The notified chemical contains functionalities with high dissociation constants, making measurement of partition coefficient in its non-ionised forms impractical under normal environment conditions.
Test Facility Harlan (2010a)

Surface Tension 59.6 mN/m at 22.6 °C

Method	EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Concentration: 9.25×10^{-2} g/L Determined using the ring method. Based on the determined surface tension of <60 mN/m, the test substance is regarded as being surface active under the conditions of the test guidelines.
Test Facility	Harlan (2011a)

Adsorption/Desorption – screening test Log K_{oc} = 4.46 and 1.99

Method	The notified chemical contains functionalities which would be ionised under the experimental conditions and interact with the column stationary phase, making measuring of its adsorption/desorption constants by HPLC impractical. The notifier provided adsorption coefficient values of 4.47 and 4.06, calculated by using KOCWIN (v2.0, US EPA 2009; in Harlan 2011d) with MCI and Pow methods, respectively.
Remarks	It is noted that the notifier's calculation did not consider the measured log Pow value of 2.10. Therefore, more accurate values of the adsorption coefficient, 4.46 and 1.99 were calculated using KOCWIN (v2.0, US EPA 2012) with MCI and Pow methods, respectively, based on the measured log Pow value of 2.10.
Test Facility	Harlan (2011d)

Dissociation Constant pKa = 10.91 and 11.56

Method	The notified chemical has low water solubility, making direct measuring of its dissociation constants impractical. When conducting the n-octanol/water partition coefficient the pKa was estimated by ACD/l-labs Web service (ACD/pKa 8.03).
Remarks	The notified chemical contains two basic groups with calculated pKa values of 10.91 and 11.56.
Test Facility	Harlan (2010a)

Flash Point 147 ± 2°C at 101.325 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Determined using closed cup equilibrium method.
Test Facility	Harlan (2011b)

Autoignition Temperature 248 ± 5°C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Determined by injecting the test substance into heated flasks and observing ignition. Flames were observed at 248°C and above.
Test Facility	Harlan (2011b)

Explosive Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties
Remarks	The chemical contains no functional groups that would infer explosive properties.
Test Facility	Harlan (2011b)

Oxidizing Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks	The chemical contains no functional groups that would infer oxidising properties.
Test Facility	Harlan (2011b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure
Species/Strain	Rat/Sprague-Dawley
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1F	300	0/1
2	1F	550	0/1
3	1F	2000	1/1
4	1F	550	0/1
5	1F	2000	1/1
6	1F	550	1/1
7	1F	175	0/1
8	1F	550	1/1

LD50	550 mg/kg bw
Signs of Toxicity	Clinical signs of toxicity were observed in all animals and include hunched posture, lethargy, ataxia, decreased respiration rate, laboured respiration, piloerection, and pallor of the extremities. Surviving animals appeared normal six to eleven days after dosing.
Effects in Organs	No abnormalities were observed in the animals that survived to the end of the study. Haemorrhagic or abnormally red lungs, dark liver, dark kidneys and slight haemorrhagic gastric mucosa were observed in some of the mortalities.
Remarks - Results	No mortalities were observed at 175 or 300 mg/kg bw dose levels, but 2/4 mortalities were observed at 500 mg/kg bw and all animals died at 2000 mg/kg bw.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	SafePharm (2008)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test
Species/Strain	Rat/Wistar
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	5M	2000	0/5
2	5F	2000	0/5

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	Signs of dermal irritation included slight to well-defined erythema and

	very slight to slight oedema. Skin observations included light brown discolouration, crust formation, haemorrhage of dermal capillaries, blanching of the skin, and scabs.
Signs of Toxicity - Systemic	None
Effects in Organs	None

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY Harlan (2012)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	For the first rabbit, three sites were treated with 0.5 mL of undiluted test substance. The sites were evaluated at 3 minutes, 1 hour and 4 hours. The other two rabbits were treated with 0.5 mL of undiluted test substance at a single site and evaluated at 4 hours. There were no significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2.0	2.0	2.0	2	<7 days	0
Oedema	2.0	1.7	2.3	3	<7 days	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal (4 hour exposure).

Remarks - Results

The pH of the undiluted test substance was 10.4.

3 minute exposure period

Very slight erythema was observed at 48 hr, with well-defined erythema and slight oedema at 72 hr. Other skin reactions included blanching at 72 hr, moderate desquamation at 7 days, and glossy skin at 14 days.

1 hour exposure period

Very slight erythema was observed at 24 hr, with well-defined erythema and very slight oedema at 48 hr, and well-defined erythema, slight oedema, and skin blanching at 72 hr. Crust formation was observed at 7 days, and the skin appeared normal at 14 days.

4 hour exposure period

Erythema (ranging from very slight to well defined in severity) and oedema (ranging from very slight to moderate in severity were observed in all treated skin sites up until the 72 hour observation. Other observations on some skin sites between day 1 and day 7 included scabbing, crust formation, discolouration, loss of skin elasticity and flexibility, and moderate desquamation. The treatment sites appeared normal by day 14.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY	Harlan (2011e)

B.4. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	Non-guideline study (similar to OECD TG 439 In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method)
Remarks - Method	The study aim is to evaluate the skin irritation potential of the test substance using the EPISKIN reconstructed human epidermis model. The test determines the level of cytotoxicity caused by the test substance to the reconstructed epidermis by measuring the colour change in the reduction reaction of yellow MTT tetrazolium salt (3[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) to a blue formazan salt that occurs in the mitochondria of viable cells. Samples of the reconstructed epidermis were treated in triplicate for 15 mins with either the test substance, Dulbecco's phosphate buffered saline (PBS) with Ca^{2+} and Mg^{2+} as the negative control, or 5% w/v sodium dodecyl sulphate as the positive control. Each sample was then removed from the wells and rinsed using the negative control solution to remove residual test substance. Following a 42 hr post-exposure incubation period, MTT solution was added and incubated with the tissue for 3 hours. The optical density at 540 nm was measured using a spectrophotometer. The relative mean viability was determined as the percentage of the optical density measurements in the treatment samples relative to the negative control samples.
RESULTS	
Remarks - Results	The mean relative viability for the test substance treated samples was 80.7%. The mean relative viability for the positive control samples was ≤40%. The study report considered the test material a non-irritant when the mean relative viability is >50% (consistent with OECD TG 439). Based on this criterion, the test substance is considered to be a non-irritant.
CONCLUSION	The notified chemical is a non-irritant to reconstructed human epidermis, under the conditions of the study.
TEST FACILITY	Harlan (2011f)

B.5. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 435 In Vitro Membrane Barrier Test Method for Skin Corrosion
Remarks - Method	Sulphuric acid (95-98%) was used as the positive control and citric acid (10%) was used as the negative control. No significant protocol deviations.
RESULTS	
Remarks - Results	The test substance produced an immediate colour change in the compatibility test and is therefore appropriate for use in the test system. In the membrane barrier test, no colour change was observed after 4 hours in four replicates, thus the test substance is considered non-corrosive.
CONCLUSION	The notified chemical is non-corrosive under the conditions of the membrane barrier test.

TEST FACILITY Harlan (2011g)

B.6. Irritation – eye (in vitro)

TEST SUBSTANCE Notified chemical

METHOD
Species Bovine corneas from freshly slaughtered cattle
Remarks - Method The age of the animals and the corneal thicknesses were not reported. Undiluted ethanol was used as the positive control. No other significant protocol deviations.

RESULTS

	In Vitro Irritancy Score (IVIS)
Test substance	66.0
Negative control	1.9
Positive control	67.4

Remarks - Results The positive control value was within two standard deviations of the historical mean of the test facility. The IVIS for the test substance was ≥55.1 and therefore the test substance is considered positive for corrosivity or severe irritation to the eye.

CONCLUSION The notified polymer is considered to be corrosive or severely irritating to the eye under the conditions of the study.

TEST FACILITY Harlan (2011h)

B.7. Irritation – eye (in vitro)

TEST SUBSTANCE Notified chemical

METHOD Non-guideline
Remarks - Method Synthetic human corneal epithelium samples were treated with 30 µL of test substance for 10 minutes. The ability of the test substance to penetrate the synthetic corneal samples was measured by reduction of MTT by viable (i.e., surviving) cells, which is considered indicative of irritation. Negative (containing 0.142 g/L Na_2HPO_4, 1.802 g/L glucose, 7.149 g/L HEPES, 0.224 g/L KCl and 7.597 g/L NaCl) and positive (2% w/v sodium dodecyl sulphate) controls were also conducted.

The optical density at 540 nm was measured using a spectrophotometer. The relative mean viability was determined as a percentage of the optical density measurements in the treatment samples relative to the negative control samples. Irritants are considered to have a mean relative tissue viability of <60.

RESULTS
Remarks - Results The mean relative viability for the test substance treated samples was 52.6%, thus the test substance is considered to be an irritant. The mean relative viability for the positive control samples was 22.2%.

CONCLUSION The notified chemical is considered an eye irritant under the conditions of the study.

TEST FACILITY Harlan (2011i)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/ CBA/Ca
Vehicle	Acetone:olive oil (4:1)
Remarks - Method	A preliminary screening study was conducted using single mice at 10, 25% or 100%. A concurrent positive control was not conducted but recent positive control studies conducted by the laboratory demonstrated the sensitivity of the laboratory. No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1068	-
2.5	14765	13.82
5	28049	26.26
10	40981	38.37

Remarks - Results	Animals treated at 25 and 100% in the preliminary study were killed on days 4 and 1 respectively, due to clinical signs of toxicity including hunched posture, lethargy, ataxia, decreased respiratory rate, splayed gait and ptosis. Body weight loss was also observed in these animals. Toxicity was not observed at 10% concentration, thus it was selected as the highest concentration for the main study. In the main study, no toxicity was observed at any concentration but mild redness to the head, neck and ears was noted in the animals treated at 10%. A dose-related positive response (stimulation index >3) was observed in all treatment groups.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Harlan (2011j)

B.9. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/Wistar
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	Arachis oil
Remarks - Method	Behavioural, functional and sensory assessments were conducted weekly. The animals were sacrificed at 28 days and half (5/sex/dose) were subject to standard test guideline pathological analyses, with the other half (5/sex/dose) subject to neuropathology. Tissues analysed for neuropathology include the brain (olfactory bulb, forebrain, cerebrum, midbrain, cerebellum, pons and medulla oblongata), dorsal rot ganglia, dorsal and ventral root fibres, eyes, optic nerve, sciatic nerve, tibial nerve, calf muscle, and the spinal cord. Recovery groups (5/sex/dose) were administered the test substance for 28 days at 0 or 20 mg/kg bw/day. Urinalysis was conducted.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10M + 10F	0	0/20
low dose	10M + 10F	5	0/20
mid dose	10M + 10F	10	0/20
high dose	10M + 10F	20	1*/20
control recovery	5M + 5F	0	0/10
high dose recovery	5M + 5F	20	0/10

* Killed *in extremis*

Mortality and Time to Death

One female treated at 20 mg/kg bw/day was killed *in extremis* on day 27 based on the severe clinical observations. Piloerection, tiptoe gait, dehydration and hunched posture were noted in the week before the mortality. The animal was emaciated and hypothermic on day 27. Histopathological examination could not determine a cause for the poor health of this animal. It is unclear whether this was treatment related.

Clinical Observations

Salivation immediately after dosing on day 25 was observed in some males and females and in one female and three males on day 27 treated at 20 mg/kg bw/day. Staining around the snout was observed in one male and one female treated at 20 mg/kg bw/day on day 22 and piloerection and hunched posture was also observed in this female. No clinical signs of toxicity were observed in animals treated at 5 or 10 mg/kg bw/day.

Behavioural, Functional and Sensory Observations

Open field arena observations confirmed the clinical signs observed in the 20 mg/kg bw/day female killed *in extremis*. Piloerection and tonic convulsions were observed during week 4 in one female treated at 20 mg/kg bw/day. No behavioural observations were observed at 5 or 10 mg/kg bw/day.

In functional tests, statistically significant decreases in overall activity were observed in males treated at 10 and 20 mg/kg bw/day during week 2 and in overall mobility for females treated at 20 mg/kg bw/day during week 3. Slight but statistically significant decreases in forelimb grip strength was observed in males treated at 20 mg/kg bw/day from the neuropathology group during week 3 and more notable statistically significant decreases were observed in males treated at 10 and 20 mg/kg bw/day during week 4. Statistically significant decreases in overall activity were observed in males treated at 20 mg/kg bw/day during the first week of the recovery period but not during the second week. A slight but statistically significant decrease in forelimb strength in males treated at 20 mg/kg bw/day was observed during the first week of recovery with a slight statistically significant increase observed in females at 20 mg/kg bw/day.

The only sensory assessment finding possibly attributed to treatment was a lower score for pupil reflex in the female killed *in extremis*.

Bodyweights, Food Consumption and Water Consumption

There were no statistically significant changes in absolute body weights. There were no statistically significant changes in body weight gain for males or females over the 28 day treatment period. However, there were statistically significant decreases in body weight gains in males and females over some single weekly intervals, mostly during weeks 3 and 4. Some decreases were observed in the 5 mg/kg bw/day dose group. Treatment groups gained weight at statistically increased levels upon cessation of treatment, demonstrating recovery. The female killed *in extremis* showed body weight losses during weeks 3 and 4.

There were no statistically significant changes in absolute food consumption or food efficiency (ratio of bodyweight gain to absolute consumption) but there were slight decreases in males and females treated at 20 mg/kg bw/day from week 2 onwards, with slight increases in these groups observed over the recovery period. A similar pattern was observed with water consumption.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were numerous statistically significant changes in haematological parameters in animals treated at 20 mg/kg bw/day, including decreases in haemoglobin, red blood cells, haematocrit, mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), mean cell volume (MCV), platelets, and increases in

white blood cells (neutrophils and lymphocytes) and clotting time. Some parameters were statistically significant at 10 mg/kg bw/day (mean cell haemoglobin concentration in males and females, and clotting time in females only). The only statistically significant changes in the recovery groups were increases in reticulocytes in males and females treated at 20 mg/kg bw/day and increases in white blood cells (neutrophils and lymphocytes) in males only. Overall, changes in haematological parameters were small and within or close to expected values for this strain of rat, thus are considered to be of low toxicological significance. The study authors note that the changes in erythrocyte and reticulocytes counts, haemoglobin, haematocrit, MCH, MCHC and MCV suggest and effect on the haematopoietic system but also note that these parameters mostly returned to normal after recovery and there were no associated microscopic changes.

There were statistically significant decreases in total protein in animals treated at 20 mg/kg bw/day (↓24%/↓22%; males/females) with slight but statistically significant decreases in males treated at 5 and 10 mg/kg bw/day. There was a slight but statistically significant decrease in the total protein in recovery males (↓7%) and a statistically significant increase in the recovery females (↑14%). There were statistically significant decreases in glucose levels in animals treated at 20 mg/kg bw/day (↓27%/↓20%; males/females) but no changes were observed in the recovery groups.

Albumin was statistically decreased in animals treated at 20 mg/kg bw/day (↓19%/↓19%; males/females), with small statistically significant decreases in males treated at 5 and 10 mg/kg bw/day in the main study. The only statistically significant change in albumin/globulin ratio was an increase in females treated at 20 mg/kg bw/day in the main study. No changes were noted in either parameter in the recovery groups.

There were statistically significant decreases in cholesterol in all treatment levels in the main study, most notably in the 10 (↓60%/↓75%; males/females) and 20 mg/kg bw/day (↓82%/↓84%) treatment groups. Slight but statistically significant changes were observed in males and females treated at 5 mg/kg bw/day. In the recovery groups, cholesterol was statistically increased in females only (↑40%). Aspartate aminotransferase was statistically increased in both sexes treated at 20 mg/kg bw/day (↑51%/↑56%) with a statistically significant increase in alanine aminotransferase in females only (↑136%), in the main study only. Alkaline phosphatase was statistically significantly increased in females treated at 20 mg/kg bw/day (↑88%).

The following statistically significant changes were observed: decreases in urea in females (10 and 20 mg/kg bw/day treatment groups), increases in potassium in both sexes in the 20 mg/kg bw/day treatment group, decreases in triglycerides in both sexes in the 10 and 20 mg/kg bw/day treatment groups, increases in chloride in males, and γ-glutamyl trans-peptidase in males. Statistically significant decreases of calcium in the main study in both sexes and increases in recovery females were relatively small.

Urinalyses revealed a statistically significant decrease in urine volume in males treated at 20 mg/kg bw/day, with a non-statistically significant decrease observed in females treated at 20 mg/kg bw/day. These changes possibly reflect the observed slight decrease in water consumption.

Effects in Organs

Organ weight changes include statistically significant increases in absolute and relative kidney weights in females treated at 10 and 20 mg/kg bw/day. There were statistically significant increases in absolute and relative brain weights in males treated at 10 and 20 mg/kg bw/day in the neuropathology groups, which is considered to be a sporadic finding as there were no brain weight changes observed in the main groups, noting that these two groups were treated identically. In the recovery groups, statistically significant increases in absolute and relative spleen weights were observed in males and in absolute and relative liver weights in females.

Macroscopic findings were observed in the lungs. Speckled appearance of the lung was observed in one female treated at 20 mg/kg bw/day in the main study. Patchy pallor of the lungs was observed in one female treated at 10 mg/kg bw/day in the main study, and in two males and one female in the recovery groups.

Microscopic alterations were noted in numerous organs (see following Table). In the heart, minimal to slight focal to multifocal myocardial necrosis with inflammatory infiltrate were noted in 4 males treated at 20 mg/kg bw/day and was only observed in a single male after the recovery period but was also observed in a single control male after the recovery. Additionally, the effect was observed in 2 recovery females (minimal to slight severity).

The effects in the lung were reported as aggregations of foamy macrophages (alveolar macrophages in the

Table) in females treated at 5 mg/kg bw/day and above and in males treated at 10 mg/kg bw/day and above.These effects were associated with alveolar wall hyperplasia by accumulation of type II macrophages at a peribronchiolar location at 10 and 20 mg/kg bw/day. Some of the animals also developed subacute to chronic alveolitis. Most findings in the lung did not resolve after 14 days recovery. Alveolar macrophages were also observed at minimal to slight severity in the main and recovery control groups.

In the liver, eosinophilic cytoplasm with a fine granular structure was observed in females treated at 10 and 20 mg/kg bw/day and in males treated at 20 mg/kg bw/day. Hepatocellular hypertrophy (centrilobular or diffuse) of minimal to slight severity was observed in males at all treatment levels, accompanied by increased hepatocellular apoptosis (mainly centrilobular). Recovery was observed, with the exception of a single occurrence of hypertrophy in the male recovery group.

In the kidney, eosinophilic cytoplasm with a fine granular structure was observed in males and females treated at 20 mg/kg bw/day. Hyaline inclusions were observed in males but were not considered treatment related due to occurrence in controls. This effect is possibly treatment related in females treated at 20 mg/kg bw/day. Observations in the recovery males were not considered treatment related.

Diffuse follicular hypertrophy in the thyroids was observed in males treated at 10 and 20 mg/kg bw/day with a single incidence in the recovery group.

In the adrenals, effects were noted at 10 and 20 mg/kg bw/day. Cytoplasm of zona fasciculata cells showed a fine granular eosinophilic appearance with apoptosis and atrophy (minor severity) observed in most animals. Atrophy and apoptosis was also observed in a 10 mg/kg bw/day female. Increased vacuolation was observed in males treated at 10 and 20 mg/kg bw/day.

In the mesenteric and cervical lymph nodes, increased hystiocytosis was observed in males and females treated at 10 and 20 mg/kg bw/day, with some occurrences in the mesenteric lymph nodes of females after recovery. Hyperplasia was observed in the mesenteric lymph nodes in the main and recovery groups with increased incidence and severity but it is unclear whether this is treatment related based on observations in control groups.

Atrophy/involution of the thymus was observed in males treated at 20 mg/kg bw/day but there were no observations following recovery.

		Main study (mg/kg bw/day)				*Recovery (mg/kg bw/day)*	
	Sex	*0*	*5*	*10*	*20*	*0*	*20[a]*
Heart (5/dose)							
myocardial necrosis with inflammatory infiltrates	M	0	0	0	4 (1.3)	1 (2.0)	1 (1.0)
	F	0	0	1 (1.0)	0	0	2 (1.5)
Lung (5/dose)							
alveolar macrophages	M	2 (2.0)	2 (1.0)	5 (2.6)	5 (3.0)	2 (1.0)	5 (2.8)
	F	2 (1.0)	5 (1.4)	5 (3.0)	5 (3.0)	4 (1.0)	4 (3.0)
alveolar hyperplasia	M	0	1 (1.0)	2 (1.5)	5 (1.6)	0	5 (1.6)
	F	0	0	5 (2.0)	5 (1.6)	0	4 (1.8)
alveolitits	M	0	0	2 (1.5)	2 (1.0)	1 (1.0)	1 (1.0)
	F	1 (2.0)	1 (1.0)	3 (1.0)	4 (1.0)	0	0
Liver (5/dose)							
eosinopohilic cytoplasm, hepatocellular	M	0	0	0	5	0	0
	F	0	0	3	5	0	0
hypertrophy, hepatocellular	M	0	2 (1.0)	4 (1.0)	5 (1.8)	0	1 (1.0)
	F	0	0	0	0	0	0

increased apoptosis	M	0	0	0	4 (1.0)	0	0
	F	0	0	0	3 (1.0)	0	0
Kidneys (5/dose)							
hyaline inclusions in tubular cells	M	4 (1.0)	3 (1.0)	3 (1.0)	5 (1.8)	3 (1.0)	3 (1.3)
	F	0	0	0	5 (1.4)	0	0
eosinophilic cytoplasm	M	0	0	0	4	0	0
	F	0	0	0	2	0	0
Thyroid (5/dose)							
follicular hypertrophy	M	0	0	3 (1.0)	3 (1.7)	0	1 (1.0)
	F	0	0	0	0	0	0
Adrenals (5/dose)							
fasciculata, apoptosis	M	0	0	0	4 (1.5)	0	1 (1.0)
	F	0	0	1 (1.0)	5 (1.2)	0	0
fasciculata, atrophy	M	0	0	0	5 (1.4)	0	1 (2.0)
	F	0	0	1 (2.0)	5 (1.0)	0	0
fasciculata, eosinophilic cytoplasm	M	0	0	0	5	0	0
	F	0	0	0	5	0	0
zona fisciculata, vacuolation	M	0	0	2 (1.0)	5 (1.4)	3 (1.0)	2 (1.5)
	F	1 (1.0)	0	0	0	0	3 (2.3)
Cervical lymph nodes (5/dose)							
increased sinusoidal histiocytes	M	0	0	1 (1.0)	2 (1.5)	0	0
	F	0	0	1 (1.0)	1 (1.0)	0	0
hyperplasia	M	0	0	0	2 (1.0)	0	0
	F	1 (1.0)	0	0	2 (1.0)	0	0
Mesenteric lymph nodes (5/dose)							
increased sinusoidal histiocytes	M	0	0	2 (1.0)	5 (2.0)	0	0
	F	0	0	3 (1.3)	5 (1.8)	0	2 (1.0)
hyperplasia	M	1 (1.0)	4 (1.0)	3 (1.3)	3 (1.3)	2 (1.0)	4 (1.0)
	F	2 (1.0)	0	4 (1.0)	5 (1.8)	1 (1.0)	2 (1.5)
Thymus (5/dose)							
atrophy/involution	M	0	0	0	5 (1.2)	0	0
	F	1 (1.0)	0	0	0	0	0

( ), average severity in affected animals, where applicable: 1=minimal, 2=slight, 3=moderate, 4=marked.
[a] female killed *in extremis* not included.

There were no treatment related histopathological findings in the neuropathology groups.

Remarks – Results

The study pathologist stated that the effects in the adrenals, liver, heart and lymph nodes (cervical and

mesenteric) are possible indications of phospholipidosis. The pathologist also noted that the effects observed in the lung were observed at all treatment levels in females and were not all fully reversibly at the high dose, thus a NOAEL could not be established in the study.

The relevance of the necrotic effects observed in the heart of males remains unclear as functional implications were not investigated in this study.

CONCLUSION
The NOAEL was not established based on histopathological effects in the lungs in females at all treatment levels. The LOAEL was 5 mg/kg bw/day.

TEST FACILITY Harlan (2010b)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test
Plate incorporation and Pre-incubation procedures

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Acetone
Remarks - Method	A range-finding study was conducted with strains TA100 and WP2uvrA in the presence and absence of metabolic activation between 0.15-5000 µg/plate. The main study was conducted using the plate incorporation (Test 1) and pre-incubation methods. The criteria for determining a positive result are a dose-related increase in mutation frequency, reproducible statistically significant increase over more than one concentration, 2-fold increase over concurrent controls, and an increase over historical controls.

RESULTS

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

Remarks - Results There were no statistically significant increases in the mutation frequency of treated plates over concurrent controls. The positive controls produced satisfactory responses, thus confirming the sensitivity of the study.

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

TEST FACILITY Harlan (2011k)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 476 In Vitro Mammalian Cell Gene Mutation Test
Cell Type/Cell Line	Mouse lymphoma/L5178Y
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Ethanol
Remarks - Method	A range-finding study was conducted in the presence and absence of metabolic activation at concentrations of up to 2850 µg/mL. The 24 hour exposures plates were only conducted in the absence of metabolic activation because there was no prior data to infer any unique metabolic requirements for the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0, 25, 75, 150, 250, 300	4 hours	48 hours	10-14 days
Test 2	0, 5, 10, 15, 25	24 hours	48 hours	10-14 days
Present				
Test 1	0, 25, 75, 150, 250	4 hours	48 hours	10-14 days

Positive controls: methyl methanesulfonate (without metabolic activation), 7,12-dimethylbenzanthracene (with metabolic activation)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test*	*Cytotoxicity* in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥150	≥150	none reported	negative
Test 2	≥15	≥15	none reported	negative
Present				
Test 1	≥150	≥100	none reported	negative

* ≤10% relative survival

Remarks – Results	There were no statistically significant increases in mutant frequency in the plates treated with the test substance. The positive controls produced a positive response, thus confirming the sensitivity of the test.
CONCLUSION	The notified chemical was not mutagenic to mouse lymphoma cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BioRelaince (2011a)

B.12. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In Vitro Mammalian Chromosome Aberration Test
Cell Type/Cell Line	Chinese Hamster Ovary Cells
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Ethanol
Remarks - Method	A range-finding study was conducted in the presence and absence of metabolic activation at concentrations of up to 2850 µg/mL. No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 21.9, 43.8, 87.5, 175*, 350, 700*, 1400, 2000*, 2850, MMC*	4 hours	20 hours

Test 2	0*, 6.5, 11.7, 21.9, 43.8*, 87.5, 125*, 175, 280*, 350, 500, MMC*	20 hours	20 hours
Present			
Test 1	0, 6.5, 11.7, 21.9, 43.8, 87.5, 175, 350, 700, 1000, CP	4 hours	20 hours
Test 2	0, 175*, 350, 500, 700*, 1000, 1400, 2000*, 2850, CP	4 hours	20 hours

*Cultures selected for metaphase analysis.
MMC, Mitomycin C. CP, Cyclophosphamide monohydrate

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test*	*Cytotoxicity* in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥2850	≥2000	none reported	negative
Test 2	≥285	≥280	none reported	negative
Present				
Test 1	≥285	>1000	none reported	not tested
Test 2	-	≥2000	none reported	negative

* ≥50% cell growth inhibition

Remarks - Results	There were no statistically significant increases in structural or numerical aberrations in the treated plates. The positive controls produced a positive response, thus confirming the sensitivity of the test.
CONCLUSION	The notified chemical was not clastogenic to Chinese hamster ovary cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BioReliance (2011b)

B.13. Genotoxicity – in vivo

TEST SUBSTANCE

METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test
Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Vehicle	Arachis oil
Remarks - Method	In the range-finding study, rats (5/sex/dose) were administered the test substance by gavage at 300, 400 or 600 mg/kg bw.

Group	*Number of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control	5/sex	0	24
vehicle control	5/sex	0	48
low dose	5/sex	100	24
mid dose	5/sex	200	24
high dose	5/sex	400	24
high dose	5/sex	400	48
positive control, CP	5/sex	50	24

CP, cyclophosphamide

RESULTS

Doses Producing Toxicity	In the range-finding study, 1/5 males and 2/5 females treated at 600 mg/kg bw died. Piloerection occurred at all doses and lethargy occurred at 400 and 600 mg/kg bw/day. In the main study, piloerection and lethargy were observed in animals treated at 400 mg/kg bw.All 100 and 200 mg/kg bw animals, and vehicle and positive control animals appeared normal during the study.
Genotoxic Effects	There were no statistically significant increases in micronucleated

	polychromatic erythrocytes. The positive controls produced a positive response, thus confirming the sensitivity of the test.
Remarks - Results	Based on the systemic toxicity observed in the study and the evidence of systemic absorption in the repeat dose study, the notified chemical is considered to have reached systemic circulation and perhaps the bone marrow.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* micronucleus test.
TEST FACILITY	BioReliance (2011c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	TOC analyser for measuring of CO_2 and dissolved organic carbon (DOC)
Remarks - Method	Conducted in accordance with the above guideline. However, the test substance was found to be poorly soluble in water. In the water solubility pre-study, an oily layer of test material on the water surface was observed. Considering the difficulties in determination of the biodegradability of organic compounds with low water solubility, the standard method for preparation of the test concentration was modified. The test substance was adsorbed onto an inert support prior to dispersion in the test vessels.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation(DOC)*	*Day*	*% Degradation(DOC)*
6	0	6	68
14	0	14	68
21	3	21	77
28	35	28	82
29	44	29	79

Remarks - Results	All validity criteria for the test were satisfied. The toxicity control attained 68% on the 14th day, thereby confirming that the test material was non-toxic to sewage sludge micro-organisms.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Haran (2010c)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test, Static
Species	Fathead Minnow (*Pimephales promelas)*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	38-46 mg $CaCO_3$/L
Analytical Monitoring	Oxygen meter TOC analyser for measuring of total organic carbon
Remarks – Method	Conducted according to the test guideline with slight modifications as discussed below: 1) The definitive tests were conducted using water accommodated fractions (WAF) test solutions containing humic acid at the concentration of 0, 10 and 20 mg/L. A WAF primary stock solution of 100 mg/L was prepared by adding a measured amount of the notified chemical in a

measured volume of dilution water with 0, 10, 20 mg/L humic acid. The dispersions were stirred for 3 hours and adjusted to pH 7.0. An oily film was observed on the surface of the stock solutions. The soluble portion of the stock solutions was removed by siphon and used to prepare the test solutions by dilution of the stock WAFs.

2) The average weight of the fish tested for this study was 0.15 g, not within the size range of 0.5 to 2.0 g required by the protocol. However, this deviation is not considered to have a negative impact on the interpretation of the study since the fish biomass to solution ratio of 0.10 g/L did not exceed the maximum required ratio of 1.0 g/L.

3) In this study, the fish were not fed for 24 hours before initiation, deviating from the protocol of not being fed during the final 48 hours before the test or during the 96-hour toxicity test. This deviation is not considered to have a negative impact on the interpretation of the study since all water quality parameters remained within acceptable ranges for the survival of fish.

RESULTS

0 mg/L humic acid

Nominal Concentration *(% WAF of 100 mg test substance/L)*	*Number of Fish*	*Mortality (%)*				
		2 h	*24 h*	*48 h*	*72 h*	*96 h*
control	10	0	0	0	0	0
6.3	10	0	0	0	0	0
13	10	0	0	0	0	0
25	10	0	0	0	0	0
50	10	0	90	100	100	100
100	10	100	100	100	100	100

10 mg/L humic acid

Nominal Concentration *(% WAF of 100 mg test substance/L)*	*Number of Fish*	*Mortality (%)*				
		2 h	*24 h*	*48 h*	*72 h*	*96 h*
control	10	0	0	0	0	0
6.3	10	0	0	0	0	0
13	10	0	0	0	0	0
25	10	0	0	0	0	0
50	10	0	0	0	0	0
100	10	0	0	0	0	0

20 mg/L humic acid

Nominal Concentration *(% WAF of 100 mg test substance/L)*	*Number of Fish*	*Mortality (%)*				
		2 h	*24 h*	*48 h*	*72 h*	*96 h*
control	10	0	0	0	0	0
6.3	10	0	0	0	0	0
13	10	0	0	0	0	0
25	10	0	0	0	0	0
50	10	0	0	0	0	0
100	10	0	0	0	0	0

LC50

	LC50 at 96 hours *(% WAF of 100 mg test substance/L)*
0 mg/L humic acid	35 (95% confidence interval: 25-50% WAF)
10 mg/L humic acid	> 100
20 mg/L humic acid	> 100

NOEC

	NOEC at 96 hours *(% WAF of 100 mg test substance/L)*

0 mg/L humic acid	25
10 mg/L humic acid	50
20 mg/L humic acid	100

Remarks – Results

The results are reported as a percentage of stock WAF rather than mg/L as the actual concentration of the notified chemical in the test solutions were not determined. As the water solubility of the notified chemical is less than 100 mg/L of the reported stock WAF concentration, the actual concentration of the notified chemical in the test solutions is expected to be equal to or less than % WAF ×100 mg test substance/L.
Surface waters tend to have higher total organic content (TOC) and dissolved organic content (DOC) than what is used in standard (OECD) aquatic toxicity testing media. Due to this, the aquatic hazard may be over-estimated in laboratory testing. In order to correct for this observed effect, mitigated endpoints were used for the classification of fish toxicity.

CONCLUSION

Not harmful to fish in environment waters with typical levels of total organic carbon.

TEST FACILITY

Springborn (2007a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 202 *Daphnia* sp. Acute Immobilisation Test –Static

Species: *Daphnia magna*
Exposure Period: 48 hours
Auxiliary Solvent: None
Water Hardness: 140 mg $CaCO_3$/L
Analytical Monitoring: pH and oxygen meter
Remarks - Method: The definitive tests were conducted in accordance with the guidelines above in WAF test solutions. A WAF primary stock solution of 100 mg/L was prepared by adding measured amount of the notified chemical in measured volume of dilution water followed with stirring for 10 minutes and adjusting the pH to 7.1. A slightly oily layer formed on the surface of the stock solution. The WAF test solutions were prepared from serial dilution of the primary stock solution. It was not reported if the dilution WAFs were prepared from the soluble part siphoned from the stock solution.

RESULTS

Nominal Concentration (% WAF of a 100 mg test substance/L)	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
0.010	5	0	0
0.026	5	0	0
0.064	5	0	0
0.16	5	0	0
0.4	5	0	2.5
1.0	5	0	5

LC50: 0.4% of a WAF prepared at 100 mg test substance/L at 48 hours (95% confidence interval: 0.16– 1.0% of WAF).
NOEC: 0.064% of a WAF at 48 hours
Remarks - Results: The test was conducted using WAFs by serial dilution of a stock WAF at 100 mg/L instead of preparing individually as described by the protocol. The results are reported as a percentage of the stock WAF as analytical testing was not conducted to verify the test concentration of the notified

chemical. As the water solubility of the notified chemical is 86.4 mg/L, the concentration of the notified chemical in the 100 mg/L of stock WAF is expected to be ≤ 100 mg/L. Therefore, the 0.4% of WAF is expected to be ≤ 0.4 mg notified chemical/L. As there was no measured concentration, these results should be treated with caution.

CONCLUSION The notified chemical is very toxic to aquatic invertebrates

TEST FACILITY Springborn (2007b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test

Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours
Concentration Range	Nominal: 0.032, 0.10, 0.32, 1.0, 3.2 and 10 mg/L Actual: not determined
Auxiliary Solvent	None
Water Hardness	~ 4.8 mg $CaCO_3$/L
Analytical Monitoring	Microscope with a hemacytometer
Remarks - Method	The test was conducted in accordance with the guidelines above with the following deviations from the protocol: 1) In the definitive test, pH change between the initial control solution and the 96-hour control solution was 2.2 units, greater than the protocol suggested change of 1.5 units. This deviation is not expected to affect the study result given that the cell density in the control cultures increased by a factor 16 times within the 72-hour test period. 2) The total organic carbon (TOC) was not measured in culture medium to initiate the test. This deviation did not impact the study results based on the monthly test results for the medium.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
0.14 (95% confidence limits: 0.089-0.25)	0.032	> 10	0.032

Remarks - Results Since there was no reduction on growth rate greater than 50% within the tested concentration range, the 72-hour E_rC50 value was estimated to be 17 mg/L by extrapolation using a linear regression. The results presented here were based on nominal concentrations as no suitable analytical method was available for the measurement of the test substance concentration in water over the desired range of concentration. All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is harmful to algae on an acute basis, but is considered to be very toxic to algae with long lasting effects.

TEST FACILITY Springborn (2007c)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 100, 180, 320, 560, 1000 mg/L Actual: not determined
Remarks – Method	Conducted according to the guidelines above with no significant deviations from the protocol.
RESULTS	
EC50	500 mg/L (95% confidence interval: 460 – 550 mg/L)
NOEC	180 mg/L
Remarks – Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified chemical is not expected to inhibit microbial respiration
TEST FACILITY	Harlan (2011l)

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