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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Phosphoric acid, *P,P'*-1,4-phenylene *P,P,P',P'*-tetraphenyl ester

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

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

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

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/1678	Fibrisol Service Australia Pty Ltd	Phosphoric acid, *P,P′*-1,4-phenylene *P,P,P′,P′*-tetraphenyl ester	No	≤ 40 tonnes per annum	Flame retardant in enclosures for professional electronic/electrical equipment

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

Human Health Risk Assessment
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 low hazard and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations
CONTROL MEASURES

Occupational Health and Safety

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

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

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

Emergency procedures

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

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

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 flame retardant in enclosures for professional electronic/electrical equipment, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment, including evidence of increasing environmental load in Australia.

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

No additional secondary notification conditions are stipulated.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Fibrisol Service Australia Pty Ltd (ABN: 57 063 405 121)
53-59 Summer Close
HEATHERTON VIC 3202

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are not varied.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU, US, Canada, Japan, Korea, New Zealand, Philippines and Taiwan

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Fyrolflex Sol-DP

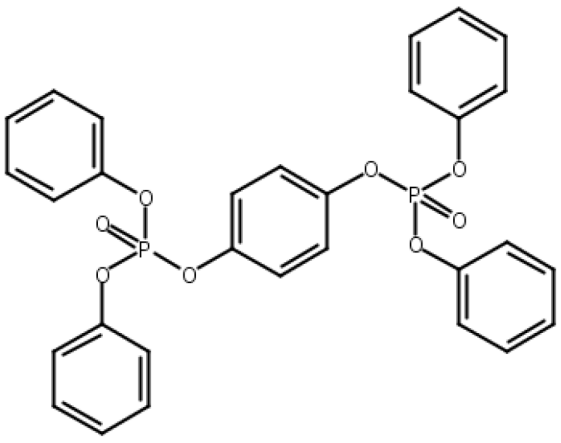
CAS NUMBER
51732-57-1

CHEMICAL NAME
Phosphoric acid, *P,P′*-1,4-phenylene *P,P,P′,P′*-tetraphenyl ester

OTHER NAME(S)
Tetraphenyl *p*-phenylene diphosphate
Aryl Bisphosphate
E-AF098T

MOLECULAR FORMULA
$C_{30}H_{24}O_8P_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
574.45 g/mol

ANALYTICAL DATA
Reference NMR, IR, HPLC/UV, LC/MS, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

IMPURITIES

Chemical Name	Phosphoric acid, triphenyl ester		
CAS No.	115-86-6	*Weight %*	0.198
Hazardous Properties	Aquatic Acute 1, H400 Very toxic to aquatic life Aquatic Chronic 2 H411 Toxic to aquatic life with long lasting effects (information provided by the notifier)		
Chemical Name	Phosphoric acid, bis[4-[(diphenoxyphosphinyl)oxy]phenyl] phenyl ester		
CAS No.	157868-60-5	*Weight %*	1.99
Chemical Name	Phosphoric acid, 4-hydroxyphenyl diphenyl ester		
CAS No.	56806-74-7	*Weight %*	0.787
Chemical Name	Phosphoric acid, *P,P′*-1,4-phenylene *P, P′*-diphenyl *P,P′*-bis[4-[(diphenoxyphosphinyl)oxy]phenyl] ester		
CAS No.	171508-72-8	*Weight %*	0.0953

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: light yellow pastilles

Property	***Value***	***Data Source/Justification***
Melting Point	102.2 °C	Measured
Boiling Point	Decomposed at > 360 °C	Measured
Density	1,347 kg/m^3 at 20 °C	Measured
Vapour Pressure	< 1 × 10^{-8} kPa at 20 and 25 °C	Measured
Water Solubility	0.0187 × 10^{-6} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Significant hydrolysis in the environmental pH range (4-9) is not expected based on the very low water solubility.
Partition Coefficient (n-octanol/water)	log Pow = 4.98	Measured
Adsorption/Desorption	log Koc = 4.91	Measured
Dissociation Constant	Not determined	Significant dissociation in the environmental pH range (4-9) is not expected based on the very low water solubility.
Particle Size	Range is 0.631 to 416.869 µm d_{10} = 4.545 µm d_{50} = 47.027 µm d_{90} = 147.189 µm	Measured (Mastersizer, summary only provided)
Particle Size	Range is > 1,000 µm to < 63 µm	Measured

Property	*Value*		*Data Source/Justification*
Particle Size (Imported Pastilles)	Diameter:		Information provided by the notifier
	≥ 6.3 mm	< 2%	
	≥ 2.5 to < 6.3 mm	> 90%	
	< 1.25 mm	< 5%	
Solid Flammability	Not highly flammable		Measured
Autoignition Temperature	> 102 °C		Measured
Explosive Properties	Unlikely to be explosive		Estimated based on the structure
Oxidising Properties	Not an oxidising substance		Measured

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported at 100% concentration as "dust-free" pastilles, containing < 5% small particles (< 1.25 mm diameter in size).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	5	10	15	25	40

PORT OF ENTRY
Sydney, Melbourne

IDENTITY OF RECIPIENTS
Fibrisol Service Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in 25 kg bags and transported by road or rail in Australia.

USE
The notified chemical will be used as a flame retardant at ≤ 12% concentration in plastic, which will be used to make enclosures for electronic and electrical equipment. The enclosures will be for professional and industrial equipment, most commonly where industry flammability standards apply. They will not be used to enclose household equipment. The notified chemical will be used as an additive in plastics such as ABS (Acrylonitrile/Butadiene/Styrene), Polycarbonate/ABS, and PPO [Poly(p-phenylene oxide)]/HIPS (High Impact Polystyrene).

OPERATION DESCRIPTION
A typical scenario to make the plastic enclosures is through compounding and extrusion, followed by formation of the articles. The notified chemical will be compounded into the final mix or into a masterbatch by mixing it with polymers and other additives in a molten state, which then undergoes an extrusion process. Thermal moulding may also be used to produce the plastic articles.

Compounding and masterbatch production
The imported pastilles containing the notified chemical at up to 100% concentration will be compounded with polymers and other materials through processes involving weighing and transferring into a mixer, heating, mixing, extruding, QA testing, dispensing of granules of the resultant compounded product or masterbatch into 25 kg drums, and routine cleaning and maintenance. The mixing and extrusion will be performed in an enclosed system.

End use
The compounded plastic or masterbatches containing the notified chemical will be blended with other pelleted materials and extruded or thermally moulded to form plastic articles containing the notified chemical at ≤ 12%. QA testing and routine cleaning and maintenance will also occur. The extrusion or moulding process to produce the finished articles is expected to be performed in a controlled area with local exhaust ventilation.

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)*
Stevedores	2-3	10-15
Transport	6	260
Warehousing	6	260
Compounding/masterbatch production	8	260
Product QC	0.5	260
Industrial users	8	260

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical at up to 100% concentration only in the unlikely event of an accident.

Compounding/masterbatch production
This process is expected to be largely enclosed and automated; however, workers may have dermal and ocular exposure to the notified chemical at up to 100% concentration when weighing and transferring the imported pastilles to the mixer, during quality control testing and during maintenance and cleaning tasks. The pastilles are "dust-free" containing < 5% small particles (< 1.25 mm diameter in size). Therefore the potential for inhalation exposure from the imported pastilles in solid form would be greatly reduced. According to the notifier, personal protective equipment (PPE) including respiratory protection, chemical resistant gloves, safety goggles, safety shoes and protective clothing are expected to be worn by workers, and should reduce worker exposure.

End-use
Processes for the production of plastic articles are expected to be largely automated; however, dermal, ocular and inhalation exposure to the notified chemical at ≤ 12% concentration may occur during transfer of the product containing notified chemical to the extruder or moulding machine, during quality control testing and during maintenance and cleaning tasks. According to the notifier, exposure is expected to be minimised by the use of local exhaust ventilation and the use of personal protective equipment (PPE) such as coveralls, impermeable gloves, eye protection and a respirator (if required). Once blended into the plastic articles, the notified chemical will be contained within the plastic matrix and is not expected to be available for exposure.

6.1.2. Public Exposure

Direct exposure
The notified chemical is for industrial use only. Therefore the public may be exposed to the notified chemical (at up to 100% concentration) only in the event of a transport accident. The public may have incidental contact with manufactured plastic enclosures (articles) in which the notified chemical will be already incorporated in the plastic matrix at ≤ 12%. The notifier indicated that the potential for blooming of the notified chemical (leaching to the surface of articles) is expected to be low, based on a study provided (see Appendix A). The direct exposure of the public to the notified chemical is expected to be very low.

Indirect exposure
The ingestion of dust/soil is considered a major potential source of indirect human exposure to chemicals. The potential for exposure via ingestion would be greater for young children because they are more likely to ingest soil than adults. As a result of behavioural patterns during childhood, and inadvertent dust ingestion among young children may occur through mouthing of objects or hands. An analogue chemical (Phosphoric acid, *P,P'*-1,3-

phenylene *P,P,P',P'*-tetraphenyl ester, CAS number 57583-54-7), which is known as RDP, is also used in electric and electronic equipment. RDP and related chemicals (which may be its impurities or breakdown products) were detected in dust samples on electronics at 431 µg/g median concentration (Ballesteros-Gómez et al, 2016). RDP was also detected in house dust in South China at 0.06 ng/g median concentration (Tan et al, 2018). This information suggests that there could be low level public exposure to the notified chemical and its impurities/breakdown products through indoor and/or outside dust. Based on the use information (enclosures to be used for professional and industrial uses, and not for household products), indirect human exposure to dust containing the notified chemical is expected to be primarily outdoor, and of a low magnitude.

6.2. Human Health Effects Assessment

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

Endpoint	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LD50 > 5,000 mg/kg bw; low toxicity
Acute dermal toxicity – rabbit	LD50 > 5,000 mg/kg bw; low toxicity
Acute inhalation toxicity – rat	LC50 > 5.23 mg/L/4 hour; low toxicity
Skin irritation – rabbit	non-irritating
Eye irritation – rabbit	slightly irritating
Skin sensitisation – guinea pig, Magnusson and Kligman test	no evidence of sensitisation
Skin sensitisation – guinea pig, modified Buehler method	no evidence of sensitisation
Repeat dose oral toxicity – rat, 90 days	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test (human lymphocytes)	non genotoxic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non genotoxic
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test – rats	NOAEL > 1,000 mg/kg bw/day

Toxicokinetics, Metabolism and Distribution
No toxicokinetic data on the notified chemical were submitted. For dermal and gastrointestinal absorption, molecular weights below 100 g/mol are favourable for absorption and molecular weights above 500 g/mol do not favour absorption (ECHA, 2017). Dermal uptake is likely to be low to moderate if the water solubility is between 1-100 mg/L and may be limited if the partition coefficient (log P) values are > 4 (ECHA, 2017). Gastrointestinal absorption is also likely to be low if the partition coefficient (log P) values are > 4. Absorption of the notified chemical through the skin and gastrointestinal tract is expected to be low based on the partition coefficient (log Pow = 4.98), very low water solubility (0.0187×10^{-6} g/L) and molecular weight (> 500 g/mol).

Acute Toxicity
The notified chemical is of low acute oral, dermal and inhalation toxicity, based on animal studies carried out according to OECD Test Guidelines.

Irritation and Sensitisation
The notified chemical was non-irritating to the skin and slightly irritating to eyes when tested in rabbits.

The notified chemical is not expected to be a skin sensitiser, based on studies conducted in guinea pigs.

Repeated Dose Toxicity
A No Observed Adverse Effect Level (NOAEL) of 1,000 mg/kg bw/day (the highest dose level tested) was established for the notified chemical in a 90-day repeated dose oral gavage toxicity study in rats, based on no treatment-related toxicologically relevant findings (including absence of neurotoxicity effects which can occur in organohosphates).

This is consistent with the results in parental animals of the combined repeated dose/reproduction/developmental study mentioned below: no treatment related deaths or adverse clinical signs of toxicity, changes in body weights,

clinical chemistry and haematology, organ weights, macroscopic or microscopic effects were reported. There were no effects noted in the motor activity test or the functional observational battery, except for a reduction in vertical plane activity in high dose females, which was not reported as being statistically significant.

Mutagenicity/Genotoxicity
The notified chemical was non-genotoxic in a bacterial reverse mutation assay, an *in vitro* chromosome aberration test using human lymphocytes and in an *in vivo* mammalian erythrocyte micronucleus test in mice. However in the micronucleus test it could not be confirmed that the test substance had reached the bone marrow.

Toxicity for Reproduction
The NOAEL was established as > 1,000 mg/kg bw/day for rats in a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test (OECD TG 422). However, it was noted that this study protocol requires only limited examination of the pups.

Some effects in the male reproductive organs were noted in both this study and the 90-day repeated dose study. In this study, additional microscopic evaluation of testes and epididymides revealed no abnormalities, except for minimal epithelium degradation in the seminiferous tubules of one high dose animal (considered an incidental finding as it is commonly seen in male rats). In the 90-day repeated dose toxicity study, statistically significant increases in testes and epididymides weights by 11% and 13.5% respectively were noted in the high dose recovery group. It is not known whether the increase in organ weights was associated with histopathological changes, as they were not evaluated in recovery animals. Therefore there is some uncertainty about the reproductive/developmental toxicity effects of the notified chemical. It is noted that the analogue chemical known as RDP (Phosphoric acid, *P,P'*-1,3-phenylene *P,P,P',P'*-tetraphenyl ester, CAS number 57583-54-7), is listed on the EU Community rolling action plan (CoRAP) for evaluation as a suspected reprotoxin, suspected PBT/vPvB and potential endocrine disrupting chemical.

Health Hazard Classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Workers may be exposed to the notified chemical at up to 100% concentration during manufacture of plastic articles containing the notified chemical.

Based on the available information, the notified chemical is of low hazard, presenting only as a slight eye irritant. At the proposed handling concentrations the notified chemical may have the potential to cause some eye irritation effects. There is also some uncertainty about the reproductive/developmental toxicity effects of the notified chemical.

According to the notifier, operations to blend the notified chemical into plastic articles are expected to be carried out in well ventilated areas with enclosed and automated processes where possible. Workers are expected to wear personal protective equipment (PPE) such as coveralls, impermeable gloves, eye protection and a respirator (if required) when handling the notified chemical. These control measures should reduce exposure and the risk of adverse effects. Once blended into the plastic articles, the notified chemical will be contained within the plastic matrix and is not expected to be available for exposure.

Therefore, under the occupational settings described, the risk of the notified chemical to occupational health is not considered to be unreasonable.

6.3.2. Public Health
Members of the public may have limited exposure to plastic articles (enclosures for electronic and electrical equipment) containing the notified chemical. However, once blended into articles, the notified chemical will be contained within the plastic matrix and direct exposure of the public to the chemical is expected to be low. In addition the public is not expected to have significant contact with the enclosures, which are not for household use. Indirect exposure of the public to the notified chemical may occur through the outdoor environment dust at very low levels.

Based on the available toxicity data, and on the likely very low public exposure from the proposed use pattern, the notified chemical is not considered to pose an unreasonable risk to public health.

7. ENVIRONMENTAL IMPLICATIONS

The notified chemical is in a class of chemicals known as organophosphate ester (OPE) flame retardants which have been detected in various environmental compartments.

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported at 100% concentration and may be compounded with other materials to form masterbatches. These masterbatches will be blended with other materials and processed to form plastic articles containing the notified chemical. The masterbatch production process and the blending process are expected to be largely enclosed and automated. Any waste containing the notified chemical generated during these processes is expected to be collected for recycling or disposal by approved waste management facilities. Empty bags containing residual notified chemical are expected to be disposed of in accordance with local government regulations. Accidental spills of the notified chemical during import, transport and storage are expected to be collected for recycling or disposal of in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used as a flame retardant in enclosures for electronic and electrical equipment. It will be incorporated into the plastic matrix. Thus, release of the notified chemical during use is expected to be limited.

RELEASE OF CHEMICAL FROM DISPOSAL

The electronic and electrical enclosures containing the notified chemical are expected to be disposed of to landfill at the end of their useful lives. Used plastic equipment containing the notified chemical may enter recycling streams, but they will ultimately end up in landfill.

7.1.2. Environmental Fate

Biodegradation and bioconcentration studies conducted on the notified chemical show that it is not readily biodegradable (8% degradation after 28 days) and does not bioconcentrate in fish (whole fish BCF = 212). For details of the environmental fate studies refer to Appendix C. The notified chemical is hydrophobic and, as for other OPEs, sediment may act as a sink. Once in sediment, many OPEs are persistent (Cao et al., 2017).

Most of the notified chemical is expected to share the fate of the electronic and electrical equipment in which it is incorporated, which are expected to be disposed of to landfill at the end of their useful lives. Used plastic equipment containing the notified chemical may enter recycling streams, but they will ultimately end up in landfill. In landfill, the notified chemical will be present as part of cured solids and will be neither bioavailable nor mobile. The notified chemical is expected to be slowly degraded by biotic and abiotic processes to form water and oxides of carbon and phosphorous.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated, as release of the notified chemical to the aquatic environment will be limited based on its reported use pattern. However, in the USA where OPEs are widely used and manufactured, these substances have been detected in indoor air and dust, the atmosphere, wastewater and sludge, surface water, sediment, and biological samples (Cao et al., 2017). It is unknown whether the major source of contamination originates from manufacture or use.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. The results are presented as nominal concentrations. Details of these studies can be found in Appendix C. In addition, no effect on mortality or reproduction up to the water solubility limit of the notified chemical was reported in a 14 day range-finding chronic *Daphnia* study; however, the full study report was not provided.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LL50 > 100 mg/L (WAF)	Not harmful to fish up to its water solubility limit

Daphnia Toxicity	48 h EL50 > 100 mg/L (WAF)	Not harmful to aquatic invertebrates up to its water solubility limit
Algal Toxicity	72 h EL50 > 1,000 mg/L (WAF)	Not harmful to algae up to its water solubility limit

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

7.2.1. Predicted No-Effect Concentration (PNEC)

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated as the notified chemical is not expected to be harmful to aquatic life up to its water solubility limit.

7.3. Environmental Risk Assessment

A Risk Quotient (PEC/PNEC) has not been calculated for the notified chemical. The notified chemical is not readily biodegradable and is likely to be persistent in sediment. This may lead to an increasing environmental load. However, its release to the aquatic environment is expected to be limited based on the reported use pattern and it is not expected to be harmful to aquatic organisms up to its water solubility limit. Therefore, based on the low hazard and the reported use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment. This assessment of risk may need to be reviewed in the future, if there is evidence that increasing environmental load of the notified chemical is leading to adverse environmental effects.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 102.2 °C

Method	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature
Remarks	A Differential Scanning Calorimeter was used.
Test Facility	Kesla Forschung & Service (2007a)

Boiling Point Decomposed at > 360 °C without boiling

Method	EC Directive 92/69/EEC A.2 Boiling Temperature
Remarks	A Differential Scanning Calorimeter was used. No endothermic effects occurred that could be interpreted as boiling point.
Test Facility	Kesla Forschung & Service (2007b)

Density 1,347 kg/m^3 at 20 °C

Method	EC Directive 92/69/EEC A.3 Relative Density
Remarks	CIPAC (Collaborative International Pesticides Analytical Council) method MT3.3.2. was used.
Test Facility	GC Laboratories Ltd (2007)

Vapour Pressure < 1×10^{-8} kPa at 20 and 25 °C

Method	EC Directive 92/69/EEC A.4 Vapour Pressure
Remarks	The effusion method was used. No regression could be performed for the measured vapour pressures, as weight loss was only observed at very high temperatures. The vapour pressure was therefore estimated.
Test Facility	LAUS GmbH (2008)

Water Solubility 0.0187×10^{-6} g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Generator Column Method; the notified chemical was analysed by LC-MS/MS.
Test Facility	Wildlife International (2008)

Partition Coefficient (n-octanol/water) log P_{ow} = 4.98

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method; column temperature was maintained at 40 °C.
Test Facility	Wildlife International (2010a)

Adsorption/Desorption log K_{oc} = 4.91

Method	OECD TG 121 Adsorption Coefficient Using HPLC Method
Remarks	Column temperature was maintained at 40 °C.
Test Facility	Wildlife International (2010b)

Particle Size Ranged from > 1,000 µm to < 63 µm

Method CIPAC Methods MT 59.4

Range (µm)	*Mass (%)*
> 1,000	8.6
500-1,000	20.3
250-500	25.3
125-250	22.3

63-125	11.4
Passing 63	11.2
Loss of sieving	0.9

Remarks Changing the sieving time did not make a significant difference to the distribution.
Test Facility GC Laboratories Ltd (2007)

Solid Flammability Not highly flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids)
Remarks The test substance melted when it came into direct contact with the butane burner flame. The main test was not performed, as the material was negative in the preliminary test.
Test Facility Kesla Forschung & Service (2007c)

Autoignition Temperature > 102 °C

Method EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids
Remarks There was no exothermic event before the sample was melted. Testing above the melting point was not effective, as the sample melted and ran out of the gauze holder.
Test Facility GC Laboratories Ltd (2007)

Oxidising Properties Not an oxidising substance

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids)
Remarks The sample was ground before testing. The preliminary and main tests were both negative.
Test Facility GC Laboratories Ltd (2007)

Blooming Evaluation The blooming rate was considered low under the conditions of the test.

Method The mixture of PC/ABS (polycarbonate/acrylonitrile butadiene styrene) polymer containing the notified chemical at 10% was compounded, injection-moulded and conditioned at 70°C. Visual blooming was evaluated after 14 and 35 days. Quantitative detection of the chemical at the surface was carried out immediately after injection moulding and after 35 days. Headspace evaluation was carried out after 35 days to monitor volatilisation of the chemical.
Remarks Visible blooming was not evident at day 14 and day 35. The surface level of the notified chemical on the plastic was below 1 µg/cm^2 at day 0 and day 35 (0.43 and 0.53 µg/cm^2 respectively). The notified chemical was not detected in the headspace at day 35.

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100. "Acute Oral Toxicity", August 1998.
Species/Strain	Rat/Sprague-Dawley
Vehicle	Corn oil (suspension)
Remarks – Method	Minor protocol deviations to animal room humidity were considered not to have compromised the validity or integrity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 per sex	5,000	0

LD50	> 5,000 mg/kg bw
Signs of Toxicity	There were no clinical signs of toxicity.
Effects in Organs	At necropsy, no gross lesions were noted.
Remarks – Results	All rats gained weight during the study.

CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Experimur (2005)

B.2. Acute Dermal Toxicity – Rabbit

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity (February 1987) U.S. EPA Health Effects Test Guidelines, OPPTS 870.1200. "Acute Dermal Toxicity", August 1998.
Species/Strain	Rabbit/New Zealand White
Vehicle	None
Type of dressing	Semi-occlusive
Remarks – Method	After the 24 h application period, residual test material was removed with water-moistened gauze. Minor protocol deviations that were considered not to have an adverse effect on the validity or integrity of the study included *ad libitum* provision of the rabbit food, rather than the fixed quantity prescribed in the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 per sex	5,000	0

LD50	> 5,000 mg/kg bw
Signs of Toxicity – Local	There were no signs of skin irritation.
Signs of Toxicity – Systemic	There were no clinical signs of toxicity.
Effects in Organs	At necropsy, no gross lesions were noted.
Remarks – Results	Average bodyweight gains were observed in the rabbits during the study.

CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	Experimur (2008a)

B.3. Acute Inhalation Toxicity – Rats

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009) U.S. EPA Health Effects Test Guidelines, OPPTS 870.1300. "Acute Inhalation Toxicity", August 1998.
Species/Strain	Rat/Sprague-Dawley
Vehicle	None
Method of Exposure	Snout only exposure
Exposure Period	4 hours
Physical Form	Solid aerosol
Particle Size	

	Mass median aerodynamic diameter (MMAD)	Geometric standard deviation (GSD)
Gravimetric (µm)	6.45 – 6.93	2.228 – 2.437
Analytical (µm)	6.49 – 8.40	2.297 – 3.560

The data indicated that 15-16% of the particles were < 2.9 µm.
The MMAD achieved was considered to appropriately represent the particle size of the test substance (as supplied) when aerosolised.

Remarks – Method	Small variations in observation frequency and use of animals of different age and weight than specified in the protocol were not considered to have affect the validity or integrity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	5.0	5.23 (gravimetric) 5.17 (analytical)	0

LC50	> 5.23 mg/L/4 hours
Signs of Toxicity	Salivation was noted from 108 minutes after the start of exposure. Immediately post exposure all animals had unkempt coats and stained fur on the nose and hunched posture in all females. The animals had no abnormalities by approximately 1 hour post exposure and during the remainder of the 14-day observation period.
Effects in Organs	One male had two dark foci in the left lung lobe and another male had pinpoint dark foci in all lobes. Two males and one female had enlargement of the mandibular lymph nodes. All other animals were normal at necropsy. Ratios for lung versus body weight for all animals were considered normal by study authors.
Remarks – Results	There were some post exposure body weight losses in 3 males and 3 females followed by recovery of the weight, and all animals had gained expected body weight by day 14.
CONCLUSION	The notified chemical is of low acute toxicity via inhalation.
TEST FACILITY	Charles River Laboratories (2011)

B.4. Skin Irritation – Rabbit

TEST SUBSTANCE	Notified chemical

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (2002)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 F
Vehicle	The test substance was mixed to a paste with sterile water, just prior to administration.
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks – Method	No protocol deviations were reported. A single animal was dosed first as a preliminary test. After exposure, the treated area was cleaned with cotton wool soaked in lukewarm water.

RESULTS

Remarks – Results	No erythema or oedema was noted at any of the observations. No indications of systemic toxicity were noted. Soft faeces and mucus on the litter tray of one female at the 48 hour observation were not considered by the study authors to be related to the treatment. Body weight gain was normal.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	RTC (2008a)

B.5. Eye Irritation – Rabbit

TEST SUBSTANCE	Notified chemical
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.2400. "Acute Eye Irritation", August 1998.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	72 hours
Remarks – Method	No protocol deviations were reported. Conjunctival discharge observations were not reported. The treated eye of each animal was rinsed with water 24 h after administration of the test substance.

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	0.33	0	0	1	< 48 h	0
Conjunctiva – Chemosis	0	0	0	1	< 24 h	0
Corneal Opacity	0.3	0	0	1	< 48 h	0
Iridial Inflammation	0	0	0	0	-	0

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

Remarks – Results	There were no deaths. A score of 1 for corneal opacity was noted in one rabbit at the 24-hour observation. Conjunctival redness and chemosis (a score of 1) were noted in one rabbit at the 1-hour observation and the redness score persisted to the 24-h observation. Conjunctival chemosis (a score of 1) was observed in one rabbit at the 1-hour observation only. All effects were resolved at the 48-hour observation.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Experimur (2006)

B.6. Skin Sensitisation – Guinea Pig Magnusson and Kligman Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Magnusson and Kligman Test
Species/Strain	Guinea pig/Dunkin-Hartley
PRELIMINARY STUDY	Maximum non-irritating concentration: Intradermal: 5, 1 and 0.5% Topical: 50, 20, 5 and 1%
MAIN STUDY	
Number of Animals	Test Group: 20 F Control Group: 10 F
Vehicle	Corn oil
Positive Control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
INDUCTION PHASE	Induction concentration: Intradermal: 5% Topical: 50% The skin was treated with 10% Sodium Lauryl Sulfate (SLS)
Signs of Irritation	Moderate to severe erythema (score of 3) was observed at the sites of intradermal injection where Freund's complete adjuvant was used. Very slight erythema (score of 1) was shown at sites treated intradermally with the vehicle alone (control group). Very slight to well defined erythema (scores of 1 and 2) was observed at sites treated with the test substance (test group). No erythema was observed after 48 h at sites topically treated with either the test substance at 50% concentration or the vehicle alone. Hardening of the treated skin sites was noted in all animals of both groups. This reaction was attributed by study authors to the pre-treatment with SLS, and the subsequent dosing with the test substance or control solvent.
CHALLENGE PHASE	
Challenge	Topical: 50%
Remarks – Method	No protocol deviations were reported.

RESULTS

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

Remarks – Results	There were no deaths. Body weight changes were normal.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	RTC (2008b)

B.7. Skin Sensitisation – Guinea Pig Modified Buehler Method

TEST SUBSTANCE	Notified chemical
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.2600. "Skin Sensitisation", August 1998.
Species/Strain	Guinea pig/Hartley
MAIN STUDY	
Number of Animals	Test Group: 20 M Control Group: 10 M

Vehicle	The test material was moistened with water before being applied via a Hill Top Chamber.
Positive Control	1-chloro-2,4-dinitrobenzene (DNCB) was tested concurrently. A concentration of 0.3% in ethanol was used for induction, and 5% in acetone for the challenge dose.
INDUCTION PHASE	Induction concentration: Topical: 100%
Signs of Irritation	None
CHALLENGE PHASE	
Challenge	Topical: 100% moistened with water
Remarks – Method	Protocol deviations included the accidental use of a higher concentration of DNCB at challenge (5% instead of 0.05%) and not moistening the test substance with water during the first induction dose. The study authors considered that the deviations did not compromise the validity or integrity of the study. There was no preliminary study. A second challenge was not required based on the results of the first challenge.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st Challenge*	
		24 h	*48 h*
Test Group	100%	0/10	0/10
Control Group	100%	0/20	0/20

Remarks – Results	There were no deaths. Body weight changes were normal. It is not clear whether the accidental use of a higher concentration of the positive control DNCB at challenge may have reduced the sensitivity of the study.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Experimur (2007)

B.8. Repeat Dose Oral Toxicity – Rats

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents (1998) U.S. EPA *Health Effects Test Guidelines*, OPPTS 870.3100. "90-day Oral Toxicity in Rodents", August 1998.
Species/Strain	Rats/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: 4 weeks
Vehicle	1% methylcellulose in water
Remarks – Method	Minor protocol deviations such as variation in the ambient temperature were considered not to have an adverse effect on the validity or integrity of the study. Urinalysis was not conducted.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 per sex	0	0/20
Low Dose	10 per sex	50	0/20
Mid Dose	10 per sex	250	0/20
High Dose	10 per sex	1,000	0/20
Control Recovery	5 per sex	0	0/10

High Dose Recovery	5 per sex	1,000	1/10

Mortality and Time to Death
One female in the high dose recovery group died during week 13 due to a dosing accident.

Clinical Observations
There were no toxicologically significant clinical signs associated with exposure to the notified chemical during the study.

Bodyweight and bodyweight gains during the treatment period were slightly higher for males in the mid and high dose groups, however slightly lower for females exposed to the same doses. Bodyweight and bodyweight gains during the recovery period were slightly lower for males exposed to 1,000 mg/kg/day, possibly due to the higher bodyweight gains during treatment. These changes were not considered to be related to treatment by study authors due to the differences between the sexes and the marginal nature of the difference.

There were no treatment related findings for ophthalmic examination, motor activity, sensory reactivity and food consumption.

Laboratory Findings – Clinical Chemistry, Haematology
The haematological examination after treatment exhibited slightly elongated prothrombin times for males in the high dose group, whilst females in the mid and high dose groups showed slightly shorter activated partial thromboplastin (APTT) times. After the recovery period, male and female APTTs were shortened. All these changes were statistically significant. However, they were not considered by the study authors to be toxicologically significant.

Other statistically significant changes noted in females were reductions in mean cell haemoglobin count and mean cell haemoglobin concentration in the high dose group and reduced white blood cell counts in the mid and high dose groups. These were considered to be normal biological variation by the study authors on the basis that they were minor in inter-group differences from controls or lacked a clear dose response or were attributed to individual outliers. These haematological parameters were not measured in the recovery animals.

Slightly high cholesterol (in the mid and high dose males) and triglyceride (in the mid dose males) concentrations were observed in the biochemical examination of the blood plasma in week 13. However, these changes did not show a dose response and the effects disappeared after the recovery. Therefore this finding was not consider to be toxicologically significant by the study authors. Small changes in mean urea and glucose levels in high dose females were observed with some other changes in blood chemistry, and considered these to be due to biological variation.

Effects in Organs
Statistically significant increases in mean testes and epididymides weights by 11% and 13.5% respectively compared to controls were seen in recovery males (4/5), but not in the main group. Histopathology was not carried out on these tissues in the recovery group, therefore any related effects in tissues was not examined. These changes were not considered as toxicologically significant by the study authors.

Remarks – Results
There were no other treatment related findings reported as a result of macroscopic and microscopic examinations. However, not all tissues were examined in macropathology, including testes.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1,000 mg/kg bw/day by the study authors, based on that no treatment related deaths or significant toxicity was observed at this dose.

TEST FACILITY Huntingdon Life Sciences (2011a)

B.9. Genotoxicity – Bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (July 1997)

	EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure (test 1)/Pre incubation procedure (test 2)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	Liver S9 fraction from rats pre-treated with β-naphthoflavone and phenobarbitone
Concentration Range in Main Test	With or without metabolic activation: 0, 313, 625, 1,250, 2,500 and 5,000 µg/plate
Vehicle	Dimethylsulfoxide (DMSO)
Remarks – Method	No protocol deviations were reported.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5,000			
Test 1		> 5,000	≥ 1,250	negative
Test 2		> 5,000	≥ 1,250	negative
Present	> 5,000			
Test 1		> 5,000	≥ 1,250	negative
Test 2		> 5,000	≥ 1,250	negative

Remarks – Results	The test substance did not induce increases in the number of revertant colonies in the plate incorporation or pre-incubation assay, at any dose level, in any tester strain, in the absence or presence of S9 metabolism. The concurrent positive and negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	RTC (2008c)

B.10. Genotoxicity – *In Vitro* Chromosome Aberration Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (1997) EC Directive 2000/32/EC B.10 Mutagenicity – *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	Liver S9 fraction from rats pre-treated with phenobarbital and 5,6-benzoflavone. 2% v/v S9 was used in Test 1, and 5% in Test 2.
Vehicle	DMSO
Remarks – Method	No protocol deviations. No preliminary test was conducted. The positive controls used wee cyclophosphamide (+S9) and mitomycin C (-S9).

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 12.77, 21.28, 35.47, 59.12, 98.53, 164.22, 273.69*, 456.16*, 760.26*, 1,267.10	3 h	18 h
Test 2	0, 50, 100, 200, 400*, 600, 800, 1,000*, 1,200, 1,267.10*	21 h	21 h
Present			

Test 1	0, 12.77, 21.28, 35.47, 59.12, 98.53, 164.22, 273.69*, 456.16*, 760.26*, 1,267.10	3 h	18 h
Test 2	0, 50, 100, 200, 400, 600*, 800, 1,000*, 1,200, 1,267.10*	3 h	18 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in: Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 1,267.10	≥ 760.26	negative
Test 2	> 1,267.10	≥ 800	negative
Present			
Test 1	> 1,267.10	≥ 760.26	negative
Test 2	≥ 1,267.10	≥ 800	negative

Remarks – Results

The test substance caused no statistically significant or biologically relevant increases in the proportion of cells with chromosomal aberrations at any concentration in the absence and the presence of S9 mix.

There were no statistically significant increases in polyploid metaphases during metaphase analysis in both tests.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the validity of the test.

CONCLUSION

The notified chemical was not clastogenic to human lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY

Huntingdon Life Sciences (2011b)

B.11. Genotoxicity – *In Vivo* Mammalian Erythrocyte Micronucleus Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test (July 1997)

Species/Strain: Mouse/CD-1®(ICR)

Route of Administration: Oral – gavage

Vehicle: Corn oil

Remarks – Method: No protocol deviations.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5 M	0	24 h
	5 M		48 h
II (low dose)	5 M	500	24 h
III (mid dose)	5 M	1,000	24 h
IV (high dose)	5 M	2,000	24 h
	5 M		48 h
V (positive control, CP)	5 M	80	24 h

CP = cyclophosphamide

RESULTS

Doses Producing Toxicity

The test substance did not induce signs of clinical toxicity in the animals treated at dose levels up to 2,000 mg/kg bw.

The test substance was also not cytotoxic to the bone marrow as no statistically significant decrease in the PCE:NCE ratios was observed at any dose level.

	Statistically higher values were observed for PCE:NCE ratios in the positive control group and in the test substance dose group at 500 mg/kg bw but no at other two doses. Therefore, these higher values observed were not considered to be biologically significant by study authors.
Genotoxic Effects	The test substance did not induce statistically significant increases in micronucleated PCEs at any dose level.
Remarks – Results	The positive control caused the expected increase in micronucleated cells, confirming the validity of the test system. However toxic signs or indications of bone marrow toxicity were not seen at the highest dose. Therefore it cannot be confirmed that the test substance reached the bone marrow.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.
TEST FACILITY	Covance Laboratories Ltd (2007)

B.12. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test – Rats

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (March 1996)
Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 35 days minimum (M), approximately 54 days (F) Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	1% methylcellulose in solvent (not reported)
Remarks – Method	The histopathology protocol was revised to include an additional staining procedure, to allow detailed examination of one testis and one epididymis from 5 males in the high dose and control groups. These tissues were processed through a glycol methacrylate blocks, sectioned and stained with PAS/H (Periodic Acid-Schiff/Hematoxylin) with special emphasis on stages of spermatogenesis and interstitial testicular cell structure. Minor protocol deviations, including occasional variation in humidity, and mishandling of one tissue with a gross lesion (enlarged bronchial lymph nodes) were considered by study authors not to have compromised the validity or integrity of the study. No urinalysis was conducted. On postnatal day 0, the sex for rat pups was determined and a gross external physical examination was conducted. Dead or stillborn pups were examined for gross external abnormalities and when feasible (for fresh un-autolysed pups), a visceral examination was performed.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 per sex	0	0
Low Dose	10 per sex	50	0
Mid Dose	10 per sex	250	0
High Dose	10 per sex	1,000	0

Control Recovery	5 per sex	0	0
High Dose Recovery	5 per sex	1,000	0

Mortality and Time to Death (Parental animals)
There were no deaths.

Clinical Observations (Parental animals)
No clinical signs during the treatment and recovery periods were noted except scattered cases of alopecia, scabs, lacrimation and red material around the eyes during the treatment.

No adverse treatment related changes were noted for food consumption, body weights, body weight gains, mating and pregnancy.

No adverse changes related to the test substance treatment in the motor activity and functional observation battery tests were noted. Reduced vertical plane activity in high dose females was seen, however this was not reported as statistically significant.

Laboratory Findings – Clinical Chemistry, Haematology (Parental animals)
No treatment related clinical chemistry and haematology parameters were noted. Some sporadic changes in clinical chemistry (such as decreased chloride concentrations and increased lactate dehydrogenase and aspartate aminotransferase levels in the low dose group males and decreased blood urea nitrogen levels in the high dose recovery males) were noted, that were not consistent or dose related. In the haematology parameters, relative reticulocyte levels were statistically significantly higher in treated recovery females. Raised absolute haematological values (not statistically significant) were observed in recovery and treated females. There were also some isolated changes in the differential white blood cell count in males and females at all treatment groups.

Effects in Organs (Parental animals)
No changes in organ weights and gross pathology that were considered treatment related were observed.

Microscopic evaluation was conducted in testicle and epididymis sections of control and high dose (not for the recovery group) parental males by staining with PAS/H, with special emphasis on stages of spermatogenesis and interstitial testicular cell structure. One male rat in the high dose group showed minimal degeneration of the germinal epithelium of the seminiferous tubules. This microscopic change was minimal, characterised by sporadic tubules being lined only by Sertoli cells, and is commonly seen in male rats; therefore, it was considered unrelated to treatment by the study authors.

Reproduction/Developmental Toxicity Outcome
No adverse treatment related changes were noted for reproductive performance, litter viability or litter weights. All results from visceral examination on six stillborn foetuses (3, 1, and 2 from the vehicle control, mid and high dose groups respectively) were reported by study authors to be normal. No dose related changes were seen in the sex ratio of the pups. Individual data were not presented in the study report.

Remarks – Results
During the study, no treatment related deaths or adverse clinical signs of toxicity, changes in body weights, clinical pathology, organ weights, motor activity or the functional observational battery were reported. There were no effects on reproductive performance, litter viability or pup body weights.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as > 1,000 mg/kg bw/day by the study authors, the highest dose tested, based on the absence of treatment related adverse effects at that dose.

TEST FACILITY Experimur (2008b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	Activated sludge from a domestic STP
Exposure Period	28 days
Auxiliary Solvent	Dichloromethane
Analytical Monitoring	Oxygen consumption by electrode
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was first dissolved in dichloromethane (1 g/L) before adding to the test bottles. The solvent was then allowed to evaporate by placing the bottles on a roller bank in a ventilated hood for more than 12 hours before the test water was added.

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
7	0	7	69
14	3	14	80
28	8	28	-

Remarks – Results	A toxicity control was not run. The other validity criteria for the test were satisfied.
CONCLUSION	The test substance is not readily biodegradable
TEST FACILITY	Akzo Nobel (2007a)

C.1.2. Bioaccumulation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 305 Bioconcentration: Flow-through Fish Test
Species	*Lepomis macrochirus* (bluegill)
Exposure Period	Exposure: 60 days Depuration: 18 days
Auxiliary Solvent	Dimethylformamide (DMF)
Concentration Range	Nominal: Solvent control, 0.017 µg/L Actual: < Limit of Quantitation (LoQ), 0.00947 µg/L
Analytical Monitoring	Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
Remarks – Method	A limit test was run with no major deviations from the test guidelines. A primary stock solution of 17 µg/mL was prepared in DMF. A dispensing stock solution of 0.17 µg/mL was prepared from the primary stock and injected into the diluter mixing chamber where it was mixed with well water to achieve the test concentration. The solvent control was achieved by injecting DMF into the diluter mixing chamber at the same rate. Water and fish samples were collected on days 0, 1, 4, 7, 14, 21, 28, 42 and 60 of the uptake phase, and on days 1, 3, 7 and 14 of the depuration phase for chemical analysis.
RESULTS	
Bioconcentration Factors	Edible tissue BCF = 122 Non-edible tissue BCF = 292 Whole fish BCF = 212

Remarks – Results	All validity criteria for the test were satisfied. Dissolved oxygen (DO) concentration in the test water was ≥ 7.2 mg/L at 22°C (≥ 82% air saturation; USGS, 2011) during the test. BCF was calculated based on mean measured concentrations.
CONCLUSION	The test substance is not considered to bioconcentrate in fish.
TEST FACILITY	Wildlife International (2013)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish - Static
Species	*Danio rerio* (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	HPLC - UV
Remarks – Method	A limit test was run with no major deviations from the test guidelines. A loading rate of 100 mg/L was prepared and stirred for 40 hours before being settled overnight. The Water Accommodated Fractions (WAFs) were siphoned off from the middle of the flasks and used for testing. A loading rate of 1,000 mg/L was also prepared following the same procedure but only tested with 3 fish to confirm that the LL50 was higher than 100 mg/L.

RESULTS

Loading rate (mg/L WAF)		*Number of Fish*	*Mortality*
Nominal	*Measured*		*96 h*
Control	< LOD	7	0
100	< LOD	7	0
1,000	< LOD	3	0

LOD: Limit of detection = 0.007 mg/L

LL50	> 100 mg /L WAF at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. DO concentration in the test water was ≥ 8.3 mg/L at 23°C (≥ 97% air saturation; USGS, 2011) during the test.
CONCLUSION	The test substance is not harmful to fish up to its water solubility limit.
TEST FACILITY	Akzo Nobel (2008)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	HPLC - UV

Remarks – Method: No major deviations from the test guidelines were reported. A definitive test was run based on a preliminary test results. A loading rate of 100 mg/L test substance was prepared and stirred for 24 hours before being allowed to settle for 1 hour. The WAF was then removed for testing.

RESULTS

Loading rate (mg/L WAF)		*Number of D. magna*	*Number Immobilised*
Nominal	*Initial measured*		*48 h*
Control	< LOD	20	0
100	0.48	20	0

EL50: > 100 mg /L WAF at 48 hours

Remarks – Results: All validity criteria for the test were satisfied. DO concentration in the test water was ≥ 8.2 mg/L at 20 °C (≥ 90% air saturation; USGS, 2011) during the test.

CONCLUSION: The test substance is not harmful to aquatic invertebrates up to its water solubility limit.

TEST FACILITY: Akzo Nobel (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: 72 hours

Concentration Range: Nominal: 1, 10, 100 and 1,000 mg /L WAF
Initial measured: < LOQ, < LOQ, < LOQ and 0.119 mg/L
(LOQ = 0.02 mg/L)

Auxiliary Solvent: None

Water Hardness: Not reported

Analytical Monitoring: HPLC - UV

Remarks – Method: No major deviations from the test guidelines were reported. The proposed nominal loading rates of the test substance were separately prepared and stirred for 41 hours. The WAFs were then siphoned off from the middle of the flasks for testing. Test water was sampled at 0 and 72 hours for analysis of the test substance. A reference test with potassium dichromate was run.

RESULTS

Biomass		*Growth*	
EbL50	*NOEL*	*ErL50*	*NOEL*
(mg/L WAF at 72 h)	*(mg/L WAF)*	*(mg/L WAF at 72 h)*	*(mg/L WAF)*
> 1,000	≥ 1,000	> 1,000	≥ 1,000

Remarks – Results: All validity criteria for the test were satisfied. The mean cell densities in the control increased by 87 times after 72 hours. Potassium dichromate gave an ErC50 = 0.94 mg/L, which was within the historical range.

CONCLUSION: The test substance is not harmful to algae up to its water solubility limit.

TEST FACILITY: Akzo Nobel (2007c)

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