File No: STD/1267

30 November 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Polycyclic sulfonic acid, triammonium salt in HP inkjet cartridges

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

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

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

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Director
NICNAS

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FULL PUBLIC REPORT

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Hewlett-Packard (Australia) Ltd. (ABN 74 004 394 763)
3 Richardson Place
North Ryde, NSW 2113

NOTIFICATION CATEGORY
Standard: Chemical other than polymer.

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Ireland, Canada, United States and Japan with ongoing notifications in Switzerland, China, the Philippines and South Korea.

2. IDENTITY OF CHEMICAL

MOLECULAR WEIGHT
500-1000

MARKETING NAME(S)
HP Ink Cartridges CB319E/H/W and CB324E/H/W (products containing the notified chemical)

ANALYTICAL DATA
Reference NMR, IR, DSC, Mass Spectroscopy, GPC, UV and HPLC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY >90%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Dark purple/black powder.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	276°C (decomposes)	Measured
Boiling Point	Not determined	The notified chemical decomposed upon melting.
Density	1500 kg/m^3 at 23.4°C	Measured
Vapour Pressure	7 x 10^{-11} kPa at 25°C	Measured
Water Solubility	501 - 525 g/L at 20°C	Measured
Hydrolysis as a Function of pH	Stable at pH 4,7 and 9	Measured
Partition Coefficient (n-octanol/water)	log P_{OW} < -4.02 at 23 ± 1°C	Measured
Adsorption/Desorption	log K_{OC} <1.25 at 40°C	Measured
Dissociation Constant	pKa = -9.96 to -0.49	Estimated
Particle Size	Inhalable fraction (<100 μm): 23.6% Respirable fraction (<10 μm): 5.21%	Measured
Solid Flammability	Not highly flammable	Measured
Autoignition Temperature	>400°C	Measured
Explosive Properties	Predicted to be negative	Estimated
Surface Tension	71.9 mN/m at 22°C	Measured
Oxidising Properties	Predicted to be negative	Estimated

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported as component of the ink in inkjet printer cartridges. The notified chemical will be imported within printer cartridges and are not reformulated or repackaged before final use. Printer cartridges containing the notified polymer will be marketed under the trade names HP Ink Cartridges CB319E/H/W and CB324E/H/W .

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	<1	<1	<1	<1	<1

PORT OF ENTRY: Melbourne VIC

IDENTITY OF MANUFACTURER/RECIPIENTS
The printer cartridges containing the notified chemical will be sold to both industry and the public.

TRANSPORTATION AND PACKAGING
The notified chemical is imported in 30mL ink Cartridges. The notified chemical will be transported and stored in these cartridges prior to use. The cartridges will be transported throughout Australia via road and rail.

USE
Ingredient in ink preparations at concentrations of <5% intended for use in both commercial and personal inkjet printing on various media.

OPERATION DESCRIPTION

The notified chemical is not manufactured, reformulated or repackaged within Australia.

Transportation and Storage
The notified chemical will be imported as the finished product within inkjet printer cartridges, which are contained within sealed protective packaging.. The notified chemical will be stored and transported within these cartridges prior to use by industry and the public.

End Use
The notified chemical will be used in inkjet printer cartridges. Office workers, customer service engineers and the public are all expected to be involved in the replacement of spent printer cartridges.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Importation/dockside workers	10	4 hours/day	70 days/year
Storage and transport workers	100	6 hours/day	240 days/year
Office workers/service technicians	10000	<0.1 hours per day	20 days/year

Transport and warehouse personnel will only be exposed to the notified chemical in case of an accident involving a breach of the imported cartridges.
Dermal and inhalation exposure to the notified polymer may occur when replacing spent cartridges. However, the concentration of the notified polymer in the ink is <5%, and the design of the cartridges is such that exposure to the notified polymer should be low. Once the ink dries, the chemical would be trapped in the printed paper, and therefore dermal exposure to the notified chemical from contact with the dried ink is not expected.

6.1.2. Public exposure
Dermal and inhalation exposure to the notified polymer may occur when replacing spent cartridges. However, the concentration of the notified polymer in the ink is <5%, and the design of the cartridges is such that exposure to the notified polymer should be low. Once the ink dries, the chemical would be trapped in the printed paper, and therefore dermal exposure to the notified chemical from contact with the dried ink is not expected.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	Oral LD50 >2500 mg/kg bw Low toxicity
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw Low toxicity
Rat, acute inhalation toxicity	Not performed
Rabbit, skin irritation	Slightly irritating
Rabbit, eye irritation	Slightly irritating
Mouse, skin sensitisation – Local lymph node assay	No conclusive evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL 150 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	Non mutagenic
Genotoxicity – in vitro chromosome aberration test	Some evidence of genotoxicity
Genotoxicity – in vivo	Not performed

Toxicokinetics, metabolism and distribution

In the Repeated Dose 28-day Oral Toxicity Study and the Acute Oral Toxicity study in rats, coloured urine and faeces were observed, indicating that the notified chemical and/or its coloured metabolites are excreted via these routes. Additionally, colouration of urine indicates that the notified chemical is absorbed from the gastrointestinal tract.

Absorption of the notified chemical through the skin is expected to be very low, due to the reasonably high molecular weight of the notified chemical and its low log Pow. This is supported by the lack of acute dermal toxicity observed.

Acute toxicity.

The notified chemical is of low toxicity via the oral and dermal routes. Inhalation toxicity was not tested, based on the fact that exposure is likely to be via the dermal route.

Irritation and Sensitisation.

The notified chemical is slightly irritating to the skin and eyes. There was no conclusive evidence of sensitisation in a mouse local lymph node assay (LLNA). Similar chemicals have shown evidence of reactions indicative of skin sensitisation.

Repeated Dose Toxicity.

In a 28-day repeat dose oral gavage study, adverse macroscopic, histopathological and clinical abnormalities were confined to animals treated with 1000 mg/kg bw/day of the notified chemical. The nature of the treatment-related effects observed among animals dosed at 1000 mg/kg bw/day were estimated to be a result of the irritant characteristics of the test material. The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day based on the treatment-related effects observed among animals dosed at 1000 mg/kg bw/day.

Genotoxicity

The notified chemical was found not to be mutagenic in a bacterial reverse mutation test. There was no strong evidence of clastogenicity to human lymphocytes in vitro, although a small but statistically significant elevation in aberrations was noted after 24 hour exposure without metabolic activation. The significance of this finding cannot be confirmed as an in vivo study was not performed.

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

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Based on available data, the hazard characteristics of the notified chemical are considered to be low, however with equivocal results in one vitro genotoxicity study.

There is low potential for worker exposure to the notified chemical when replacing spent cartridges as it is at low concentration (< 5%) in the ink formulations, which are sealed within the cartridge. Service technicians may occasionally experience skin contact with the notified chemical during maintenance; however, the notified chemical is at low concentrations in the ink formulations. There is potential for inhalation exposure to the notified polymer with ~5% of the notified polymer being respirable. However, inhalation of significant amounts of the notified chemical is not expected due to its low concentration in the toner. Also the high water solubility of the notified chemical should ensure that any inhaled material is rapidly cleared from the lungs and hence the risk from inhalation of the notified chemical is low. Exposure to the notified chemical on printed-paper is low as the dye is bound to the paper matrix. Some intermittent exposure may occur if printing onto a non-absorbent substrate occurs and the ink does not dry for a time.

The notified chemical will be imported in pre-packed sealed cartridges. During transport and storage, workers are unlikely to be exposed to the notified chemical except when cartridges are accidentally breached.

Given that exposure of workers to the notified chemical is expected to be low, and the toxicological profile of the notified chemical, the risk to workers is considered acceptable.

6.3.2. Public health

The exposure and hazard of the notified chemical to the members of the public during the use of inkjet printers are expected to be similar to that experienced by office workers. Therefore, the risk of the notified chemical to the health of the public is assessed to be low. The unlikely but potential public exposure through accidents during importation, transportation or storage is assessed as very low.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

Printer ink will be imported in ready-to-use cartridges (containing <5% notified chemical). No release is expected as manufacturing and reformulation of the ink containing the notified chemical will not take place in Australia. Environmental release of the notified chemical is unlikely during importation, storage and transportation, and spillage during a transport accident is the most likely reason for environmental release. Individual container capacity, container and packaging specifications would limit the extent of release.

RELEASE OF CHEMICAL FROM USE

The ink cartridges are designed to prevent leakage and will not open during transport, use, installation or replacement. Therefore, release of ink containing the notified chemical to the environment is not expected under normal conditions of use. If ink is released from the cartridges during installation and replacement it will be contained with absorbent material and disposed of in landfill. Cartridges are contained within the printer until the contents are used then they are removed and sent to a recycling and disposal centre.

Most of the notified chemical (>98%) will be bound to the printed paper, which will be disposed of to landfill, recycled or incinerated. Recycling of treated paper may result in the release of a proportion of the notified chemical to the aquatic compartment. Waste paper is repulped using a variety of chemical treatments, which result in fibre separation and ink detachment from the fibres. The waste is expected to go to trade waste sewers. Approximately 50% of the ink printed on paper will enter paper recycling of which a proportion of the ink is expected to be recovered during recycling. While most may partition to water, due to the low percentage of the notified chemical in these inks and the widespread use, release to the aquatic compartment from any given recycling plant will still be low based on worst case assumptions. Any chemical absorbed to sludge during recycling process will be disposed of to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

The total import volume of the notified chemical will ultimately be disposed as normal office/domestic waste that will end up in either landfill or be incinerated. Some waste paper printed with the ink may be disposed of directly to landfill with the notified chemical bound to the paper. Some will enter the paper recycling process. Used cartridges will be sent to recycling and disposal centres. The cartridges will be broken down into component parts for recycling. Residual ink (< 2% of the notified chemical) left in the empty cartridges will be separated from the cartridges and incinerated during the recycling of the cartridges.

Notified chemical that is incinerated is expected to thermally decompose to form predominantly simple organic compounds and various salts. Similarly, notified chemical that is disposed of to landfill should eventually degrade.

7.1.2 Environmental fate

A single biodegradability test report was submitted which indicates that the notified chemical is not ready biodegradable. For the details of the environmental fate study please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

Manufacture, reformulation and packaging into end-use containers occurs overseas, and release is not expected. After use, printed-paper may be disposed of by incineration, to landfill or be recycled. Notified chemical disposed of to landfill, may be mobile, however, the low proposed annual import volume, and diffuse release throughout Australia will mitigate any potential exposure while the notified chemical slowly degrades.

In Australia, approximately 50% of printed-paper is recycled. The following Predicted Environmental Concentration calculation assumes this 50% recycling, and as a worst case scenario assumes no recovery within STPs.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	50.000%	
Annual quantity of chemical released to sewer	500.000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	1.37	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP	0%	
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.33	µg/L
PEC - Ocean:	0.03	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1300 kg/m^3). Using these assumptions, irrigation with a concentration of 0.334 mg/L may potentially result in a soil concentration of approximately 3.340 X 10^{-3} mg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 1.670 X 10^{-2} mg/kg and 3.340 X 10^{-2} mg/kg, respectively.

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 >100 mg/L	Not Harmful
Daphnia Toxicity	E_iC50 >100 mg/L	Not Harmful
Algal Toxicity	E_iC50 >100 mg/L	Not Harmful
Lemna minor Toxicity	E_iC50 >100 mg/L	Not Harmful
Inhibition of Bacterial Respiration	E_iC50 >1000 mg/L	Not Harmful

7.2.1 Predicted No-Effect Concentration

Aquatic ecotoxicity data were provided for three trophic levels. The following Predicted No-Effect Concentration has been calculated using an assessment factor of 100.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga).	>100.00	mg/L
Assessment Factor	100.00	
PNEC:	>1000.00	µg/L

7.3. Environmental risk assessment

Based on the above PEC and PNEC values, the following Risk Quotient (Q) has been calculated.

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	0.33	>1000	<0.00033
Q - Ocean:	0.03	>1000	<0.00003

This indicates that the current import volume and use pattern is not expected to pose an unacceptable risk to the aquatic environment.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

Human health risk assessment

Under the conditions of the occupational settings described, the risk to workers is considered to be acceptable.

When used in the proposed manner the risk to the public is considered to be acceptable.

Environmental risk assessment

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following safe work practice to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with eyes and skin.

- Service personnel should wear cotton or disposable gloves and ensure adequate ventilation is present when removing spent printer cartridges containing the notified chemical and during routine maintenance and repairs.

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

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

Public Health

- Products containing the notified chemical should be labelled with the following safety direction:
  - Avoid skin and eye contact with ink

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 an ingredient in ink preparations at concentrations of <5%, or is likely to change significantly;
- the amount of chemical being introduced has increased from 1 tonne, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 276ºC (with decomposition)

Method EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks The melting point of the test material was determined using differential scanning calorimetry. An exothermic peak was observed from 276ºC, indicative of decomposition. Decomposition was confirmed visually by performing a test using the metal block apparatus.
Similar thermographic profiles were obtained using air and nitrogen atmospheres; this indicates that the observed decomposition in both determinations is probably thermal and not oxidative.
Test Facility Safepharm Laboratories Ltd (2006a)

Boiling Point Not determined

Method
Remarks The test material was found to decompose with melting. As a result of this its boiling point was not determined.
Test Facility Safepharm Laboratories Ltd (2006a)

Density 1500 kg/m^3 at 23.4ºC

Method EC Directive 92/69/EEC A.3 Relative Density.
Remarks The relative density of the test material was determined using a gas comparison pycnometer.
Test Facility Safepharm Laboratories Ltd (2006b)

Vapour Pressure 7 x 10^{-11} kPa at 25ºC

Method EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure of the test material was determined using the vapour pressure balance method between 170-180°C and extrapolated..
Test Facility Safepharm Laboratories Ltd (2006e)

Water Solubility 501 - 525 g/L at 20ºC

Method EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method The water solubility of the test material has been determined to be between 50.1 and 52.5% w/w of solution at 20°C.
The standard A6 Method was not applicable to this test material due to the high indeterminable saturation levels produced. It was therefore not possible to prepare samples at five times the saturation level as recommended in the guideline. No analysis could be performed due to high solubility producing unfilterable mixtures and thus water solubility was estimated based on visual inspection.
Test Facility Safepharm Laboratories Ltd (2006a)

Hydrolysis as a Function of pH

Method EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

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

Remarks Analysis by HPLC. Estimated from the 50°C test.
Test Facility Safepharm Laboratories Ltd (2006b)

Partition Coefficient (n-octanol/water) log P_{OW} <-4.02 at 23.0±1.0°C

Method EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Analytical Method: HPLC
The partition coefficient of the test material was determined using the shake-flask method.
The limit value for the organic phase samples was obtained from the lowest detectable standard within the experimentally determined linearity of response range.
The test material contained strong acid salt groups and therefore pKa values were outside the environmentally relevant pH ranges for the determination of partition coefficient. As a result of this, testing was performed at pH 7 using the shake-flask method as recommended for salts.
Test Facility 2006a

Adsorption/Desorption – screening test log K_{oc} <1.25 at 40°C.

Method EC Directive 2001/59/EC C.19 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography
Remarks The method guideline states that the measurement of adsorption coefficient should be carried out on substances in their ionised and unionised forms. However, since the test material is a salt (of strong acid), testing was carried out at neutral pH. The notified chemical eluted before the reference substance Acetanilide.
Test Facility 2006b

Dissociation Constant Not determined

Method OECD TG 112 Dissociation Constants in Water.
Remarks Testing was not possible according to Method 112 of the OECD Guideline for Testing of Chemicals, 12 May 1981 due to the absence of any dissociating functional groups within the pH range of the test method.
Therefore, estimates were obtained using ACD/I-Lab Web Service (ACD/pKa 8.03), computer based estimation software.

Results:
Dissociation Constant Result pKa 1 -0.49 Sulphonic acid
pKa 2 -0.98
pKa 3 -1.19
pKa 4 -1.92
pKa 5 -9.96

It can be determined that the substance would always be ionised at environmentally relevant pH's.
Test Facility Safepharm Laboratories Ltd (2007c)

Particle Size

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (μm)	*Mass (%)*
<100	23.6
<10.2	5.21
<5.4	0.638

Remarks Measured using a cascade impactor after a preliminary sieve test.
Test Facility Safepharm Laboratories Ltd (2007b)

Solid Flammability

Method	EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks	The substance has been determined to be not highly flammable as it failed to ignite in the preliminary test.
Test Facility	Safepharm Laboratories Ltd (2006d)

Autoignition Temperature >400ºC

Method	EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks	The notified chemical did not self ignite when tested up to 400°C.
Test Facility	Safepharm Laboratories Ltd (2006e)

Explosive Properties

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Based on the chemical structure of the test material the result for the explosive properties is predicted to be negative.
Test Facility	Safepharm Laboratories Ltd (2006e)

Surface Tension 71.9 mN/m at 22ºC

Method	EC Directive 92/69/EEC A.5 Surface Tension.
Remarks	Concentration: 1000mg/L The surface tension of the test material was determined using the ring method based on ISO 304 with a White Electrical Institute interfacial tension balance. The notified chemical is considered not to be a surface-active material. Based on the information obtained in the hydrolysis as a function of pH test, negligible hydrolysis of the sample solution would have occurred during the course of the surface tension test.
Test Facility	Safepharm Laboratories Ltd (2006b)

Oxidizing Properties

Method	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	Based on the chemical structure the result for the oxidising properties has been predicted negative.
Test Facility	Safepharm Laboratories Ltd (2006e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 2004/73/EC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD
Vehicle	Distilled water
Remarks - Method	No significant protocol deviations. The 1 hour post dose observation was missed in error in the second group of animals.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	3/F	2000	0
II	3/F	2000	0

LD50	>2000 mg/kg bw
Signs of Toxicity	There were no signs of systemic toxicity. Purple-coloured urine was noted in all animals one and two days after dosing. All animals appeared normal three days after dosing.
Effects in Organs	No gross pathological changes were observed at necroscopy.
Remarks - Results	Estimated at >2500 mg/kg bw, based on the test results and the decision tree in the OECD test guideline.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories Ltd (2006f)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Sprague-Dawley CD
Vehicle	The test material was moistened with arachis oil BP.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/M	2000	0
2	5/F	2000	0

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	There were no test substance related dermal reactions.
Signs of Toxicity - Systemic	There were no deaths or test substance related clinical signs. All animals showed expected gains in body weight over the study period.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	None

CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Safepharm Laboratories Ltd (2007g)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Male
Vehicle	Test substance was moistened with distilled water.
Observation Period	7 Days
Type of Dressing	Semi-occlusive.
Remarks - Method	A 3-minute and 1-hour semi-occluded application of the test material to the intact skin of one rabbit was also tested.

RESULTS

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

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

Remarks - Results	Pink/purple coloured staining was noted at all treated sites during the study. In the main study, the only effect seen was erythema in one animal. A 3-minute and 1-hour semi occluded application of the test material to the intact skin of one rabbit produced no evidence of skin sensitisation.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Safepharm Laboratories Ltd (2006h)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White (Two different suppliers)
Number of Animals	3
Observation Period	3 days
Remarks - Method	No significant protocol deviations. The chemical was applied in powder form. The pH of a 10% aqueous solution of the notified chemical was 3.6.

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	0.67	0.67	0.67	2	48 hours	0
Conjunctiva: chemosis	0	0	0	1	1 hour	0
Conjunctiva: discharge	0.33	0	0.67	2	48 hours	0
Corneal opacity	0	0	0	0	-	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

Purple coloured staining of the fur was noted around all treated eyes throughout the study.
No corneal or iridial effects were noted throughout the study.
Moderate conjunctival irritation was noted in all treated eyes 1-hour after treatment, which was resolved by the 72 hour observation.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Safepharm Laboratories Ltd (2006i)

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

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 429 Skin sensitisation: Local Lymph Node Assay.
EC Directive 2004/73/EC B.42, Local Lymph Node Assay in the mouse.

Species/Strain: Mouse/CBA/Ca and Mouse/CBA/Ca
Vehicle: Dimethyl formamide
Remarks - Method: No significant protocol deviations.
Test concentrations were chosen on the basis of a preliminary screening test.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/Lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	718.05	
5	921.34	1.28
10	776.94	1.08
25	1206.96	1.68
Positive Control		
5		2.50
10		4.03
25		9.13

Remarks - Results

No signs of systemic toxicity were noted. Staining of the fur and ears was noted post dose day 2 and for the remainder of the study.
At a concentration of 25% the mean DPM was significantly different ($p<0.05$) to the control group. However, a stimulation index of <3 was recorded for all concentrations tested.
The stimulation index for the positive control was dose related, with positive responses observed at 10 and 25% w/w, therefore confirming the validity of the assay.

CONCLUSION

There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY Safepharm Laboratories Ltd (2006j)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

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

Species/Strain	Rat/Sprague-Dawley Crl:CD (SD) IGS BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 5-hours (weekdays), 1-hour (weekends) Dosage was adjusted to take account of the purity of the test material.
Vehicle	Distilled water
Remarks - Method	No significant protocol deviations. No recovery groups were included. Dosages were determined by a preliminary 14 day range finding study.

RESULTS

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

Mortality and Time to Death
No mortality was observed during the treatment.

Clinical Observations
Hunched posture was noted in one female on day 22 in the high dose group.
A statistically significant ($p<0.01$) decrease in female fore limb grip strength was shown but was not supported by clinical to suggest neurotoxicity.
There were no treatment related changes in the behavioural parameters measured, apart from one female in week 4, which appeared cold (hypothermia) and had a hunched posture.
There were no treatment related changes in sensory reactivity.
Males receiving 1000 mg/kg bw/day showed a statistically significant reduction in weight gain in comparison with control groups at week 1 ($p<0.01$) and week 2 ($p<0.05$).
No adverse effect on dietary intake or food efficiency was detected.
High dose females consumed approximately 40% more water during the third week of treatment than the concurrent controls. Males receiving the high dose rate remained unaffected.
Staining of the faeces and cage tray liners from day 2 is attributed to the coloured nature of the test substance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There were no treatment related changes detected in the blood chemistry.
No toxicologically significant changes were detected in the haematology. Male rats treated with 1000 mg/kg bw/day showed a slight reduction in group mean haematocrit accompanied by an increase for mean corpuscular haemoglobin concentration compared with controls. In addition male rats treated with 1000 mg/kg bw/day also showed a small reduction in prothrombin time and activated partial thromboplastin time compared with controls at the end of the treatment period. Male rats treated with 150 mg/kg bw/day showed a slight reduction for group mean haematocrit and an increase for mean corpuscular haemoglobin concentration. There were no histopathological correlates to suggest an anaemia or inhibitory effect on the intrinsic coagulation factors.
Female rats treated with 1000 mg/kg bw/day showed elevated levels of lymphocytes and platelets. However, isolated increase in lymphocytes is often stress induced.
The statistical significance for the findings was minimal ($p<0.05$) and all effects seen were considered of no

toxicological importance.

Effects in Organs
There were no treatment related changes in the organ weights measured.

Necropsy
Macroscopic abnormalities were confined to animals treated with 1000 mg/kg bw/day of the notified chemical and involved gastric inflammation characterised in the glandular epithelium by a raised limiting ridge in one of five females. Coloured contents from the test material were detected along the large intestine, caecum and rectum in both sexes treated with 1000 mg/kg bw/day of the notified chemical.

Histopathology
Agglomerations of secretion, mucosal basophilia, mucous cell hyperplasia and acanthosis/hyperkeratosis of the stomach's limiting ridge was observed in relation to treatment, for rats of either sex dosed at 1000 mg/kg bw/day. One rat of each sex dosed at 150 mg/kg bw/day also exhibited agglomeration of secretion.

Remarks – Results
The nature of the treatment-related effects observed among animals dosed at 1000 mg/kg bw/day were predominantly a result of the irritant characteristics of the test material and in the absence of supporting evidence to suggest a degenerative change were considered by the study authors to be adaptive in nature.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study on the basis of the macroscopic and microscopic changes to the stomach at 1000 mg/kg bw/day

TEST FACILITY Safepharm Laboratories Ltd (2007k)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA$^-$
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 50-5000 µg/plate b) Without metabolic activation: 50-5000 µg/plate
Vehicle	Sterile distilled water
Remarks - Method	No significant protocol deviations.

RESULTS

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

Remarks - Results
No test material precipitate was observed on the plates at any of the doses tested in either the presence or absence of S9 mix.
The vehicle (sterile distilled water) control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals

used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation. Thus, the sensitivity of the assay and the efficacy of the S9-mix were validated.

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

TEST FACILITY Safepharm Laboratories Ltd (2006l)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
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	S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver.
Vehicle	Minimum essential medium
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	≥ 1250	4 hours	24 hours
Test 2	≥ 1250	24 hours	24 hours
Present			
Test 1	≥ 1250	4 hours	24 hours
Test 2	≥ 2500	4 hours	24 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000	> 5000	>5000	Negative
Test 2		≥ 3750	>5000	Positive
Present				
Test 1	>1250	> 5000	>5000	Negative
Test 2		> 5000	>5000	Negative

Remarks - Results In Test 2 without metabolic activation (24 h exposure) the notified chemical induced small but dose-related and statistically significant increases ($p<0.05$ and $p<0.01$ respectively) in the number of cells with chromosome aberrations at 3750 and 5000 μg/mL. The increases were considered by the study authors not to have toxicological significance because there was a low vehicle control value in that group, the values were within the historical range for the exposure group and the increases were small. The aberrations did not include any marked numbers of chromatid exchange type aberrations.
No statistically significant increases in aberrations were noted in the other three test groups.
The notified chemical did not induce a statistically significant increase in the numbers of polyploid cells at any dose level in either of the exposure groups.
All vehicle (solvent) controls had frequencies of cells with aberrations

	within the range expected for normal human lymphocytes. All the positive control materials induced statistically significant increases in the frequency of cells with aberrations, indicating the satisfactory performance of the test and of the activity of the metabolising system.
CONCLUSION	The notified chemical was clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm Laboratories Ltd (2007m)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE Notified chemical.

METHOD EC Directive 92/69/EEC C.4-C Biodegradation: Determination of the "Ready" Biodegradability: Carbon Dioxide Evolution Test

Inoculum	Activated sewage sludge.
Exposure Period	28 Days.
Auxiliary Solvent	Culture medium.
Analytical Monitoring	CO_2 analysis using TOC analyser.
Remarks – Method	No significant protocol deviations.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% degradation*	*Day*	*% degradation*
1	0	1	32
6	2	6	42
14	0	14	77
22	9	22	80
28	10	28	82

Remarks – Results All test validity criteria were satisfied.

CONCLUSION The notified chemical cannot be classed as ready biodegradable.

TEST FACILITY Safepharm Laboratories Limited (2006s)

C.1.2. Bioaccumulation

CONCLUSION The notified chemical has high water solubility and a low octanol/water partition coefficient. As such it has a low degree of lipophilicity and low potential to cross biological membranes.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - semi-static, 96 hours.
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	Dechlorinated tap water.
Water Hardness	Ca. 100 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	No significant protocol deviations were reported. The limit test was conducted in parallel.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	7	0	0	0	0	0
100	104-113	14	0	0	0	0	0

LC50	>100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	Analysis of the test preparations at 0, 24 and 96 hours showed measured test concentrations to range from 104% to 113% of nominal and so the results are based on nominal test concentrations only.
CONCLUSION	The notified chemical is not harmful to Rainbow trout.
TEST FACILITY	Safepharm Laboratories Limited (2006n)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical.
METHOD	EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – 48 hours static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Reconstituted water.
Water Hardness	Ca. 250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	No significant protocol deviations were reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	10	0	0
100	102-105	20	0	0

E_iC50	>100 mg/L at 48 hours
NOE_iC	100 mg/L at 48 hours
Remarks – Results	Analysis of the test preparations at 0 and 48 hours showed measured test concentrations to range from 102% to 105% of nominal value and so the results are based on nominal test concentrations only. The test preparations were observed to be clear red/pink solutions throughout the duration of the test.
CONCLUSION	The notified chemical is not harmful to *Daphnia magna*.
TEST FACILITY	Safepharm Laboratories Limited (2006o)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical.
METHOD	EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range Nominal	0 and 100 mg/L
Concentration Range Actual	0 and 99-105 mg/L
Auxiliary Solvent	Culture medium.
Water Hardness	Not applicable as the substance was dissolved in culture medium.
Analytical Monitoring	HPLC
Remarks – Method	No significant protocol deviations were reported except that due to the coloured nature of the test substance an increase light intensity and decreased test volume was used.

RESULTS

Biomass		*Growth*	
EbC_{50} mg/L at 72 h	*NOEC mg/L*	*ErC_{50} mg/L at 0-72 h*	*NOEC mg/L*
>100	100	>100	100

Remarks – Results	Analysis of the test preparations at 0 and 72 hours showed measured test concentrations to range from 99% to 105% of nominal and so the results are based on nominal test concentrations only.
CONCLUSION	The notified chemical is not harmful to *Scenedesmus subspicatus.*
TEST FACILITY	Safepharm Laboratories Limited (2006p)

C.2.4. *Lemna minor* growth inhibition test

TEST SUBSTANCE	Notified chemical.
METHOD	Draft OECD Guideline "*Lemna* Growth Inhibition Test (April 2004)", modified for testing coloured test substances.
Species	*Lemna minor*
Exposure Period	7 days.
Concentration Range Nominal	0 and 100 mg/L
Concentration Range Actual	0 and 102-106 mg/L
Auxiliary Solvent	Culture medium
Water Hardness	Not applicable as the substance was dissolved in culture medium.
Analytical Monitoring	No significant protocol deviations were reported.
Remarks – Method	None.

RESULTS

Biomass		*Growth*	
EC_{50} Average Specific Growth Rate (frond number and dry weight) mg/L at 72 h	*NOEC Average Specific Growth Rate (frond number and dry weight) mg/L*	*EC_{50} Yield (frond number and dry weight) mg/L at 0-72 h*	*NOEC Yield (frond number and dry weight) mg/L*
>100	100	>100	100

Remarks – Results	Analysis of the test preparations on days 0 (fresh media) and Day 2, 4 and 7 (old media) showed measured test concentrations to range from 102% to 106% of nominal and hence the results are based on nominal test concentrations only.
CONCLUSION	The notified chemical is not harmful to *Lemna minor.*
TEST FACILITY	Safepharm Laboratories Limited (2006q)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge from domestic sewage treatment plant.
Exposure Period	3 hours
Concentration Range Nominal	1000 mg/L
Remarks – Method	Oxygen consumption rates and percentage inhibition values for the control, test and reference materials were measured after 30 minutes and 3 hours.
RESULTS	
IC50	>1000 mg/L
NOEC	1000 mg/L
Remarks – Results	The reference material (3,5-dichlorophenhol) gave a 3-Hour EC_{50} value of 7.4 mg/L.
CONCLUSION	The notified chemical is not harmful to activated sewage sludge micro-organisms.
TEST FACILITY	Safepharm Laboratories Limited (2006r)

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