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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

CIM-10

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

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

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

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Canon Australia Pty Ltd (ABN: 66 005 002 951)
1 Thomas Holt Drive
North Ryde NSW 2113

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Chemical Name, Other Names, CAS Number, Molecular and Structural Formulae, Spectral Data, Molecular Weight, Purity, Impurities, Import Volume, Use Details.

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)
LVC/742

NOTIFICATION IN OTHER COUNTRIES
USA (2007); UK (2007); Switzerland (2008); Japan (2008); Korea (2008); Philippines (2008)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
CIM-10
Black C-BK4 Liq.
Black C-BK4
C-BK4

MOLECULAR WEIGHT
>1000 Da

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

3. COMPOSITION

DEGREE OF PURITY >85%

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Black powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	Decomposed from ~322°C	Measured

Boiling Point	Not determined	Decomposed prior to melting
Density	1630 kg/m^3 at 19.5 ± 0.5°C	Measured
Vapour Pressure	< 2 x 10^{-8} kPa at 25°C	Measured
Water Solubility	350-360 g/L at 20°C	Measured
Hydrolysis as a Function of pH	Stable (half-life > 1 year at pH 4, 7 and 9)	Measured
Partition Coefficient (n-octanol/water)	log P_{ow} = -4.88 at 21°C	Measured
Surface Tension	71.9 mN/m (1 g/L solution) at 21.8 ± 0.2°C	Measured
Adsorption/Desorption	log K_{oc} < 1.25 at 40°C	Measured
Dissociation Constant	pKa = 6.35, 2.22, 1.62, ≤ -0.71	Calculated
Particle Size	Inhalable fraction (<100 μm): 32.3% Respirable fraction (<10 μm): 1.14%	Measured
Flash Point	Not determined	Low vapour pressure solid
Solid Flammability	Not highly flammable	Measured
Autoignition Temperature	Does not self-ignite below 400°C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not expected to be oxidising	Estimated

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

Reactivity
The notified chemical is not expected to be reactive 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 be imported as a component (<5%) of inkjet printer ink contained within sealed ink cartridges.

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
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Canon Australia Pty Ltd and office equipment retailers and offices nationwide.

TRANSPORTATION AND PACKAGING
Imported ink cartridges (5 mL – 900 mL) containing the notified chemical (each individually sealed in a plastic bag and packaged in a box) will be stored at the notifier's warehouse prior to distribution to offices and office equipment retailers nationwide.

USE
The notified chemical will be used as a component (<5%) in ink cartridges for use in inkjet printers.

OPERATION DESCRIPTION
No manufacture or reformulation will occur in Australia. Sealed ink cartridges containing the notified chemical will be distributed to commercial and retail centres and handled by service technicians, office workers or the public, who will replace spent cartridges in printers as necessary.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Importation/ Waterside	50	<8	10-50
Storage and Transport	15	<8	10-50
Office worker/ consumer	2,000,000	10 seconds/day	2
Service Technicians	100	1	170

EXPOSURE DETAILS

Storage and transport workers will only handle the sealed cartridges containing the notified chemical and therefore exposure is not expected unless the packaging is accidentally breached.

Service technicians and office workers may be exposed to the ink containing the notified chemical (<5%) when replacing used ink cartridges and repairing and cleaning ink jet printers. Dermal exposure is expected to be the most likely route of exposure. However, occasional dermal exposure during use of the printer may occur if the printed pages were handled inadvertently before the ink had dried, or if ink-stained parts of the printer were touched. Once the ink dries, the chemical would be bonded to the printed paper, and therefore dermal exposure to the notified chemical from contact with dried ink is not expected.

6.1.2. Public exposure

Home users may encounter dermal exposure to the ink containing the notified chemical (<5%) when replacing used ink cartridges similar to the exposure experienced by office workers. However, home users are expected to handle ink cartridges and print less frequently, therefore exposure is expected to be less frequent when compared to that of office workers.

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	low oral toxicity LD50 >2000 mg/kg bw
Rat, acute dermal toxicity	low dermal toxicity LD50 >2000 mg/kg bw
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOEL 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Mutagenicity – bacterial reverse mutation (incorporating Prival and Mitchell modification for azo colourants)	non mutagenic
Genotoxicity – in vitro chromosome aberration	non genotoxic

Toxicokinetics, metabolism and distribution

Many azo dyes are unlikely to be absorbed through the skin because of their size and polarity (Øllgaard, 1998). Smaller species may undergo percutaneous absorption, dependent on their properties. There was no evidence from the toxicological investigations to suggest that the notified chemical was absorbed following dermal exposure. Absorption through the skin is not expected to be significant, given its relatively high molecular weight (>500 Da), high water solubility (>10 g/L), and low partition coefficient (log P < 0). These parameters demonstrate its low lipophilicity, indicating that it is not likely to cross the stratum corneum (European Commission, 2003). However, bacterial skin microflora have been reported to be able to break down azo dyes into smaller species, which may be more readily absorbed, through azo reduction (SCCNFP, 2002).

Highly sulfonated azo dyes are generally poorly absorbed from the intestine after oral intake. However, cleavage of the azo linkage may take place in the gastrointestinal tract, through the action of azo reductases (see below). The sulfonated aromatic amines are rapidly absorbed. Given the black or brown/purple coloured urine observed in animals during the oral studies, the observed blue contents of the gastrointestinal tract and discolouration of organs in the repeat dose oral toxicity study, it is clear that the notified chemical can be absorbed, perhaps following reduction, from the gastrointestinal tract after oral exposure.

Ultimately, the metabolites of azo dyes are expected to be excreted in the urine and bile (Brown & DeVito, 1993, referenced in Øllgaard, 1998). Sulfonation of azo dyes appears to decrease their toxicity by enhancing their urinary excretion, and that of their metabolites. The coloured urine observed in many animals that had been orally administered with the notified chemical could be indicative of the urinary excretion of metabolites of the notified chemical.

A significant proportion of the notified chemical (32.3%) is of inhalable particle size (<100 µm) and only a small fraction (1.14%) is of respirable size (<10 µm). The particles of inhalable size are expected to diffuse or dissolve into the mucus lining of the respiratory tract and be retained in the mucus and then transported out of the respiratory tract.

Acute toxicity
The notified chemical was found to be of low acute oral and dermal toxicity in studies conducted on rats (LD50 > 2,000 mg/kg bw). No information on the acute inhalation toxicity was available.

Irritation and Sensitisation
The notified chemical was found to be slightly irritating to the eye, though not enough to warrant hazard classification, and non-irritating to the skin.

The notified chemical was not a skin sensitiser when tested in a mouse local lymph node assay up to a concentration of 25% (maximum concentration that could technically be applied). Therefore, the notified chemical is unlikely to cause skin sensitisation in exposed humans.

Repeat dose toxicity
The NOEL in a 28-day oral repeat dose study in rats was established as the highest dose (1000 mg/kg bw/day), based on the absence of toxicologically significant changes in the parameters measured at all dose levels. Hence, the NOAEL is considered as ≥1000 mg/kg bw/day.

Mutagenicity and Carcinogenicity
Azo dyes are a concern for their potential induction of mutagenicity and carcinogenicity, mainly through their reduction to aromatic amines in the body. Exposure to heat or sunlight has also been reported to result in breakdown of azo dyes, including some that are similar to the notified chemical (Brown and DeVito, 1993).
The notified chemical is not expected to be reductively cleaved to release any of the restricted aromatic amines specified in either the Appendix to EC Directive 76/769/EEC (EC, 2004) or the annexes of EU SCCNFP/0495/01 (SCCNFP, 2002). However, it may be degraded to form species that resemble these arylamines, some of which are suspected of being mutagenic. However, due to their significant structural modification and the suggestive negative test data of these species, the amine species may not exhibit mutagenicity.

In addition, azo dyes are known for their content of impurities, particularly for the presence of component arylamines (SCCNFP, 2002; Øllgaard *et al* 1998). The HPLC trace provided by the notifier indicates that the sample of the notified chemical contains a number of impurities that have not been identified, each present at <1%. These impurities are both more and less polar than the notified chemical and are likely to be free amine species and/or sulfonation variants. Free amines may exhibit higher toxicity than the notified chemical as they are likely to be more readily absorbed across the skin.

The notifier supplied test results showing that the notified chemical was found to be not mutagenic in bacteria (under the conditions of the Ames test used), and did not induce chromosomal aberrations in mammalian cells *in vitro*. Furthermore, the notifier also supplied a summary of test results from a study showing that the notified chemical was found to be not mutagenic using the modified Ames test for azo dyes (Prival and Mitchell, 1982). This modified test is thought to yield a greater detection of mutagenic azo dyes as it utilises a reductive pre-

incubation step (during which the azo dye is reduced to amine species) before the test is carried out.

Overall, on the basis of weight of evidence the notified chemical is not expected to be genotoxic.

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

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
Based on the data supplied, the notified chemical has no identified hazards. Dermal exposure of workers to the notified chemical should occur infrequently and be of small amounts, given the containment of the notified chemical within ink cartridges.

The level of repeat dermal exposure for service technicians and office workers handling sealed cartridges of printing inks containing the notified chemical at < 5% is not expected to be significant compared to the NOEL of 1000 mg/kg bw/day established in the 28 day rat study.

Overall, the risk presented by the notified chemical to the health and safety of workers is not considered to be unacceptable.

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 identical or similar to that experienced by office workers. Therefore, the risk of the notified chemical to the health of the public is not considered to be unacceptable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported to Australia as a component of printer ink final product in ready-to-use cartridges. No manufacturing and reformulation of the notified chemical will take place in Australia. Environmental release of the notified chemical is unlikely to occur during importation, storage and transportation.

RELEASE OF CHEMICAL FROM USE
The ink cartridges will be designed to prevent leakage and will not be opened 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. Workers at large businesses will undertake installation and replacement. If leakage or spillage does occur, the ink will be contained with absorbent material and disposed of to landfill in accordance with federal, state and local regulations.

Cartridges will be contained within the printer until the contents are consumed and then they will be removed and sent for recycling or disposed of to landfill. Around 5% of the ink containing the notified chemical will remain in “empty” cartridges.

Most of the notified chemical (95%) will be bound to printed paper, which will be disposed of to landfill, recycled or possibly incinerated.

RELEASE OF CHEMICAL FROM DISPOSAL
Around 5 wt% of the ink containing the notified chemical will remain in “empty” cartridges. The notifier will collect the used cartridges by setting up the collection boxes in general merchandising stores and post offices, etc. The collected cartridges will be sent to a subcontractor. The subcontractor will disassemble the used cartridges and recycle them as raw materials, for example, to be used to make plastic goods. The remaining ink separated from the used cartridges will be disposed of under Australian regulations. The notifier will not refill

the used cartridges for reuse. The other cartridges which are not collected will be disposed of to landfill.

Printed paper, having the notified chemical thereon will be disposed of to landfill, recycled or possibly incinerated. Recycling of treated paper may result in the release of a proportion of the notified chemical to the aquatic compartment. Waste paper is re-pulped using a variety of chemical treatments, which result in fibre separation and ink detachment from the fibres. The wastes are expected to go to trade waste sewers. Approximately 50% of the ink printed on paper will enter paper recycling and a minor proportion of the ink may be recovered during recycling in the sludge. Any quantities of notified chemical recovered with sludge during the recycling process will be disposed of to landfill.

7.1.2 Environmental fate

The notified chemical is water soluble and not readily biodegradable, and could therefore be expected to pass through sewage treatment works and disperse in receiving waters. In practice, the notified chemical can be expected to precipitate during sewage treatment and in surface waters as sparingly soluble calcium salts. Bioaccumulation is not expected as the notified chemical has high molecular weight and is water soluble. For details of the environmental fate studies please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

The PEC is estimated below based on the assumption that 50% of the imported quantity will enter paper recycling streams and be discharged in aqueous effluent following detachment from the fibre. Note that the assumption of complete release to surface water is highly conservative as the notified chemical is expected to precipitate as calcium salts.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	< 1000	kg/year
Proportion expected to be released to sewer	0.5	
Annual quantity of chemical released to sewer	< 500	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)	21.374	million
Removal within STP	0%	
Daily effluent production:	4,275	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	< 0.32	µg/L
PEC - Ocean:	< 0.032	µg/L

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	EC50 > 100 mg/L	Not harmful
Algal Toxicity	E_rC50 > 100 mg/L	Not harmful
Lemna Toxicity	EC50 > 100 mg/L	Not harmful
Inhibition of Bacterial Respiration	EC50 > 1000 mg/L	Not harmful

The results from testing indicate that the notifed chemical is not harmful to aquatic life, consistent with its water solubility. The algal test was discontinued in favour of the Lemna test because of indications that algal growth was inhibited by light absorption.

7.2.1 Predicted No-Effect Concentration

The PNEC can be estimated as outlined below by application of a 100-fold assessment factor, as data are available for three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Aquatic toxicity	> 100	mg/L
Assessment Factor	100	
PNEC:	> 1000	µg/L

7.3. Environmental risk assessment

The Risk Quotients (Q = PEC/PNEC) are tabulated below.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.32	> 1000	<0.00032
Q - Ocean	0.032	> 1000	< 0.000032

The notified chemical is not considered to pose a risk to the environment as risk quotients are well below one, even under the hypothetical worst case assumption that the notified chemical will be discharged to surface waters after detachment from paper fibres during recycling.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

Human health risk assessment

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

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

Environmental risk assessment

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical itself, however, these should be selected on the basis of all ingredients in the formulation.

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]

workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of 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(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical;

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of inkjet printer ink, or is likely to change significantly;
  - the amount of chemical being introduced has increased from one tonne per annum, or is likely to increase, significantly;
  - the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

Material Safety Data Sheet
The MSDS of products containing the notified chemical provided by the notifier was 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 Decomposed from approximately 322 °C

Method OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Differential scanning calorimetry.
Test Facility SafePharm (2007a)

Boiling Point Not determined

Remarks The boiling temperature was not determined as the notified chemical was found to decompose prior to melting (see above).
Test Facility SafePharm (2007a)

Density 1630 kg/m^3 at 19.5 ± 0.5°C

Method OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks Gas comparison pycnometer.
Test Facility SafePharm (2007b)

Vapour Pressure < 2 x 10^{-8} kPa at 25°C

Method OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined using a vapour pressure balance. Balance readings were low and variable and thus statistical analysis was not meaningful. A regression slope was imposed on a chosen data point to provide an estimate of the maximum value for the vapour pressure at 25°C.
Test Facility SafePharm (2007c)

Water Solubility 350-360 g/L at 20°C

Method OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method. The solubility was estimated by visual inspection because of difficulties with filtration at concentrations near the solubility limit.
Test Facility SafePharm (2007a)

Hydrolysis as a Function of pH Half-life at 25°C > 1 year at pH 4, 7 and 9

Method OECD TG 111 Hydrolysis as a Function of pH.
EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	*t½*
4	50	> 120 hours
7	50	> 120 hours
9	50	415 hours

Remarks At pH4 and pH 7, less than 10% hydrolysis was detected after 5 days, which is equivalent to a half-life greater than 1 year at 25°C. At pH 9, the half-life at 25°C is estimated greater than 1 year under Arrhenius plot at 50°C, 60°C and 70°C. Half-lives at pH 9 reduced to 55.8 hours at 60°C and 7.1 hours at 70°C.
Test Facility SafePharm (2007b)

Partition Coefficient (n-octanol/water) log Pow = -4.88 at 21°C

Method OECD TG 107 Partition Coefficient (n-octanol/water).
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Flask Method with analysis by HPLC. A preliminary estimate of < -4.33 was obtained from the approximate solubilities in n-octanol (< 8 mg/L) and water (> 171 g/L).
Test Facility SafePharm (2007a)

Surface Tension 71.9 mN/m at 21.8 ± 0.2°C

Method EC Directive 92/69/EEC A.5 Surface Tension.
Interfacial tension balance and procedure based on the ISO 304 ring method.
Remarks Concentration: 0.934 g/L
Not considered to be a surface active material.
Test Facility SafePharm (2008a)

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

Method OECD TG 121 Estimation of the Adsorption Coefficient on Soil and on Sewage Sludge Using HPLC.
Remarks The test substance eluted from the column before the reference substance acetanilide.
Test Facility SafePharm (2007b)

Dissociation Constant pKa_1 = 6.35, pKa_2 = 2.22, pKa_{3-4} = 1.62, $pKa_{5-7} \leq$ -0.71,

Method OECD TG 112 Dissociation Constants in Water.
Remarks The dissociation constants were estimated (ACD/pKa 8.03) as there was no pKa within the pH range of the spectrometric and titrimetric test methods. The notified chemical is a water soluble salt that is expected to be ionised in the environment.
Test Facility SafePharm (2007b)

Particle Size

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

Range (μm)	*Mass (%)*
<100	32.3
<10.0	1.14
<5.5	0.141

Remarks The fraction <100 μm was determined by passing through a sieve. The fraction <10 μm was determined using a cascade impactor, with results averaged from three separate determinations.
Too few particles were of size <10 μm to allow accurate determination of the mass median aerodynamic diameter.
Test Facility SafePharm (2007b)

Solid Flammability Not highly flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Test Facility SafePharm (2007d)

Autoignition Temperature Does not self-ignite below 400°C

Method EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks The notified chemical decomposed during the test.
Test Facility SafePharm (2007c)

Explosive Properties Not explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	The notified chemical is not considered to be explosive as it was not thermally sensitive, shock sensitive or friction sensitive. Note that during the thermal sensitivity test performed with the 2mm orifice plate, explosions were observed at approximately 80 seconds into each of the three individual tests. In each case there was damage to the tube, however, it did not fragment into three or more pieces and thus according to the test guideline, the notified chemical is not considered to be explosive.
Test Facility	SafePharm (2007c)

Oxidizing Properties Not oxidising

Method	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	Expert statement. The molecular structure of the test substance suggests that it is unlikely to have oxidising properties.
Test Facility	SafePharm (2007c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 420 Acute Oral Toxicity – Fixed Dose Method.
EC Directive 2004/73/EC B.1 bis Acute Oral Toxicity – Fixed Dose Procedure.

Species/Strain	Rat/Sprague-Dawley CD (Crl:CD(SD)IGS BR)
Vehicle	Distilled water
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	>2000 mg/kg bw
Signs of Toxicity	There were no signs of systemic toxicity. Black stained urine was noted in three animals 3 to 5 days after dosing.

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

TEST FACILITY: Safepharm (2007e)

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 (Crl:CD(SD)IGS BR)
Vehicle	Moistened with arachis oil BP
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of dermal irritation.

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

TEST FACILITY: Safepharm (2008b)

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
Vehicle	Moistened with distilled water
Observation Period	72 hr
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	No evidence of skin irritation was noted in any of the test animals throughout the study. Purple-coloured staining was observed at all treated skin sites during the study. This did not affect evaluation of the skin reactions.

CONCLUSION: The notified chemical is non-irritating to the skin.

TEST FACILITY: Safepharm (2007f)

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
Number of Animals	3
Observation Period	72 hr
Remarks - Method	No significant protocol deviations.

RESULTS

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

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

TEST FACILITY: Safepharm (2007g)

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 Skin Sensitisation (Local Lymph Node Assay).

Species/Strain	Mouse CBA/Ca (CBA/CaBkl) strain

Vehicle	1% pluronic L92 in distilled water
Remarks - Method	No significant protocol deviations. The test substance was not suitable for dosing in any of the solvents recommended in the OECD test guideline. A suitable vehicle and concentration were found with 25% test substance in 1% pluronic L92 in distilled water.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	641.31	1.0
5	594.33	0.93
10	455.42	0.71
25	477.11	0.74
*Positive Control**		
1	Not reported	1.39
10	Not reported	11.33
20	Not reported	19.34

* 2,4-Dinitrobenzenesulfonic acid, sodium salt

CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Safepharm (2007h)

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: 14 days
Vehicle	Distilled water
Remarks - Method	Doses were corrected to account for the 93.3% purity of the test substance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M, 5F	0	0
low dose	5M, 5F	25	0
mid dose 1	5M, 5F	150	0
mid dose 2	5M, 5F	300	0
high dose	5M, 5F	1000	0
control recovery	5M, 5F	0	0
high dose recovery	5M, 5F	1000	0

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

There were isolated observations of fur staining, increased salivation, noisy respiration, and

chromodacryorrhea during the study, mainly in male animals. These were not considered to be of toxicological significance. There were no other toxicologically relevant clinical effects observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were some statistically significant and dose related changes in a few blood chemistry parameters. These were not considered to be of toxicological relevance given that the mean values were within the historical control ranges.

Several animals from all dose groups (except for controls and recovery groups) showed brown/purple coloured urine. This was considered to be a result of administration of the coloured test substance and not to be of toxicological significance.

Effects in Organs

There were statistically significant changes in the absolute and relative adrenal weights of males and liver weights of females in the high dose recovery group. Considering that such effects were not observed in the non-recovery high dose group, this was not considered to be a biologically significant effect.

High dose females displayed decreased absolute and relative heart weights. Given that there was not a dose related trend in the heart weights, there was no histopathological correlates and that the values were within historical controls, such effects were not considered to be of toxicological significance.

Blue-coloured contents were observed in the gastrointestinal tract and discolouration in the kidneys, lungs and testes of several animals in the mid and high dose groups (mainly male animals). Such effects were believed to be attributed to oral administration of the coloured test substance and were not considered to be toxicologically relevant.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 1000 mg/kg bw/day in this study, based on the absence of toxicologically significant changes in the parameters measured at all dose levels.

TEST FACILITY	Safepharm (2008c)

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	Distilled water
Remarks - Method	Formulated concentrations were adjusted to allow for the purity of the test substance. 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	Negative
Present				
Test 1	> 5000	≥ 1500 in TA1535 and TA1537 > 5000 other strains	> 5000	Negative
Test 2		> 5000	> 5000	Negative

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

TEST FACILITY Safepharm (2007i)

B.8. 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.
Pre incubation procedure
Test 1 of the study utilised the standard Ames method.
Test 2 of the study incorporated the Prival and Mitchell modification for azo compounds (Prival MJ and Mitchell VD 1982).

Species/Strain
Test 1:
S. typhimurium: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA/pKM101
Test 2:
S. typhimurium: TA98, TA100

Metabolic Activation System
Test 1:
S9-mix (details not given)
Test 2:
Hamster liver homogenate metabolising system. Hamster S9 was not treated with any enzyme inducers.

Concentration Range in Main Test
a) With metabolic activation: 19.5 - 5000 µg/plate
b) Without metabolic activation: 19.5 - 5000 µg/plate

Vehicle
Water

Remarks - Method
Study summary was provided. As such, it could not be determined whether all of the appropriate modifications for the Prival and Mitchell method were performed.

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
Present				

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

Remarks - Results: The Prival-Mitchell modification positive control, Trypan Blue, used in the test induced marked increases in the frequency of the TA98 and TA100 revertant colony with metabolic activation only. Thus, the sensitivity of the assay and the efficacy of the uninduced hamster liver S9-mix was validated.

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

TEST FACILITY: Canon (2007)

B.9. 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: Chinese hamster
Cell Type/Cell Line: Chinese hamster lung (CHL/IU) cells
Metabolic Activation System: Rat liver S9-mix induced by a combination of phenobarbitone/β-naphthoflavone
Vehicle: Eagle's Minimal Essential Medium (MEM)
Remarks - Method: The purity of the test substance was accounted for in the formulations. No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 156.25, 312.5, 625, 1250*, 2500*, 5000*	6	24
Test 2	0*, 19.5, 39, 78.13*, 156.25*, 234.38*, 312.5*	24	24
Present			
Test 1	0*, 156.25, 312.5, 625*, 1250*, 2500*, 5000*	6	24
Test 2	0*, 156.25, 312.5, 625, 1250*, 2500*, 5000*	6	24

*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	>2500	>5000	>5000	Negative
Test 2	>5000	>5000	>5000	Negative
Present				
Test 1	>5000	>1250	>5000	Negative
Test 2		>5000	>5000	Negative

Remarks - Results: The test material induced toxicity to CHL cells in all exposure groups, as indicated by the elevated mitotic index values which were considered to be due to toxicity induced cell cycle delay.

The test material did not induce any statistically significant increases in the frequency of cells with aberrations or the number of polyploid cells in any of the exposure groups.

CONCLUSION	The notified chemical was not clastogenic to Chinese hamster lung cells treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm (2007j)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD, TOC and HPLC. The results tabulated below reflect BOD determination.
Remarks - Method	The notified chemical was tested at 100 mg/L.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	-0.7	7	57
14	-0.7	14	71
21	0.3	21	73
28	0.7	28	74

Remarks - Results	The test substance did not undergo any degradation as determined by HPLC.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Kurume (2007)

C.1.2. Bioaccumulation

REMARKS	Bioaccumulation was not tested. The notified chemical is not expected to bioconcentrate in fish because of its high molecular weight and high water solubility.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – semi-static. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – semi-static.
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	Spectrophotometry
Remarks – Method	The limit of quantitation was 0.88 mg/L.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	< 0.88 mg/L	7	0	0	0	0	0
100	93.9	7	0	0	0	0	0
100	93.3	7	0	0	0	0	0

LC50	> 100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	Results are expressed as nominal concentrations, as measured concentrations were close to nominal throughout the exposure period. No sublethal effects were observed.

CONCLUSION The notified chemical is not harmful to fish.

TEST FACILITY SafePharm (2008d)

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.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	Spectrophotometry
Remarks - Method	The limit of quantitation was 0.88 mg/L.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	< 0.88	20	0	0
100	94.5-96.5	20	0	0

EC50	> 100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours
Remarks - Results	The response to the positive control (potassium dichromate) was within the normal range.

CONCLUSION The notified chemical is not harmful to daphnids

TEST FACILITY SafePharm (2008e)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

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

Species	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0.1, 1, 10, 100 mg/L
Auxiliary Solvent	None
Water Hardness	Typical algal culture medium (soft water)

Analytical Monitoring	Not conducted
Remarks - Method	A range finding study only was conducted, because significant light absorption by the test substance was measured at 460 and 665 nm.

RESULTS

Yield		*Growth*	
E_yC50 mg/L at 72 h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
~ 10	Not determinable	> 100	1

Remarks - Results	The percentage inhibition of growth rate (8, 5, 15 and 36%) increased in response to concentration. Corresponding values for yield were 33, 18, 46 and 80%.

CONCLUSION The notified chemical is not harmful to the growth of green algae, notwithstanding its colour and consequent reduction in light intensity available for photosynthesis.

TEST FACILITY SafePharm (2008f)

C.2.4. Lemna growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 221 *Lemna* sp. Growth Inhibition Test.

Species	*Lemna minor*
Exposure Period	7 days
Concentration Range	Nominal: 0.1, 1, 10, 100 mg/L
Auxiliary Solvent	None
Analytical Monitoring	Spectrophotometry (LOQ 0.88 mg/L)
Remarks – Method	Test solutions were renewed on days 2 and 5.

RESULTS

Yield		*Growth*	
E_yC50 mg/L at 72 h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
> 100	100	> 100	100

Remarks - Results	The response to the positive control (3,5-dichlorophenol) was within the normal range. There was some dark colouration observed at the highest test concentration of 100 mg/L notified chemical. Nominal concentrations of the notified chemical were confirmed by analysis.

CONCLUSION The notified chemical is not harmful to duckweed.

TEST FACILITY SafePharm (2008g)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

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

Inoculum	Activated sludge from the aeration stage of the Severn Trent Water Plc

	sewage treatment plant which treats predominantly domestic sewage.
Exposure Period	3 hours
Concentration Range	Nominal: 1, 10, 100, 1000 mg/L
Remarks – Method	3,5-Dichlorophenol was used as reference material.

RESULTS

IC50	> 1000 mg/L
NOEC	1000 mg/L
Remarks – Results	The IC50 for the reference substance was 16 mg/L

CONCLUSION	The notified chemical is not harmful to the respiration of sewage sludge microorganisms.
TEST FACILITY	SafePharm (2008h)

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