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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

H-CB Sodium salt

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

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

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)
Hewlett Packard Australia Pty Ltd (ABN 74 004 394 763)
353 Burwood Hwy, FOREST HILL VIC 3131

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants, import volume and identity of recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: Acute dermal toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA, Japan, Korea, China

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
CC643Series Tricolour inkjet cartridges (products containing the notified chemical)

OTHER NAME(S)
H-CB Sodium salt
Cyan H-CB
Copper phthalocyanine direct dye salt

MOLECULAR WEIGHT
> 500 Da

ANALYTICAL DATA
Reference IR, HPLC, LC-MS and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: blue solid

Property	Value	Data Source/Justification
Melting Point	Not determined	The test substance decomposed at 315°C.
Boiling Point	Not determined	The test substance decomposed prior to melting.
Density	1740 kg/m^3 at 20°C	Measured
Vapour Pressure	< 2.4 × 10^{-8} kPa at 25°C	Measured
Water Solubility	316 – 340 g/L at 20°C	Measured
Hydrolysis as a Function of pH	$t_{½}$ > 1 year at 25°C, pH 4,7 and 9	Measured

Partition Coefficient (n-octanol/water)	log Kow = ≤ -3.17 at 21.5°C	Measured
Adsorption/Desorption	log K_{oc} < 1.25 at 30°C	Measured
Dissociation Constant	Not determined	The notified chemical is a salt and is expected to be ionised at environmental pH (4 – 9)
Particle Size	Inhalable fraction (< 100 μm): 41.6% Respirable fraction (< 10 μm): 0.417%	Measured
Flammability (solid)	Not highly flammable	Measured
Autoignition Temperature	358ºC	Measured
Explosive Properties	Not determined	Predicted negative
Surface Tension	72.6 mN/m at 21.5ºC	Measured
Oxidising Properties (solids)	Not determined	Predicted negative

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

Reactivity
The notified chemical is predicted to be stable under normal conditions of use (stated by the notifier).

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However the data above do not address all Dangerous Goods endpoints. Therefore consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a dye (< 5% concentration) in inkjet printer ink solution 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
Melbourne

IDENTITY OF RECIPIENTS
Recipients are located in Victoria.

TRANSPORTATION AND PACKAGING
The transport of ink cartridges (e.g., 5 to 900 mL) containing the notified chemical in ink at < 5% will be by road.

USE
Dye for inkjet printer inks (< 5% concentration)

OPERATION DESCRIPTION
No manufacture or reformulation will occur in Australia. Sealed ink cartridges containing the notified chemical at < 5% 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	> 1000	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. Instructions on how to replace the cartridges safely will be included with the cartridge to minimise exposure. However, occasional dermal exposure during use of the printer may occur if the printed pages are handled inadvertently before the ink dries, or if ink-stained parts of the printer are 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 to 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	LD50 > 2000mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Evaluation of Skin Irritation Potential using the EPISKIN™ Reconstituted Human Epidermis Model	non-irritating
Rabbit, eye irritation	severely irritating
Determination of Ocular Irritation Potential Using the Skinethic Reconstituted Human Corneal Epithelium Model	non-irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOEL or NOAEL was not established
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Genotoxicity – in vitro mammalian cell gene mutation test	genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic

Toxicokinetics

No toxicokinetic data were provided on the notified chemical. The notified chemical has a molecular weight > 500 Da and a water solubility of 316 to 340 g/L at 20ºC and partition coefficient (log Pow) of ≤ -3.17 at 21.5ºC. The moderately high molecular weight and hydrophilicity of the notified chemical suggest that dermal absorption is unlikely, however there may be potential for absorption across the GI tract. This is supported by the observation of blue coloured urine in animals in the repeated dose 28-day oral toxicity study in rats.

Acute toxicity
As the acute oral LD50 was > 2000 mg/kg bw in rats, the notified chemical was considered to be of low toxicity via the oral route.

Acute dermal and inhalation toxicity studies have not been submitted on the notified chemical. With respect to acute dermal toxicity study, it has been stated that absorption through the skin barrier of compounds with a molecular weight above 500 Da is expected to be low. Therefore, due to a higher (> 500 Da) molecular weight of the notified chemical, absorption through the skin barrier is expected to be low. As such, an acute dermal toxicity study was not considered necessary for the risk assessment of the notified chemical. With respect to acute inhalation toxicity study, based on formulation, use scenario and packaging, inhalation exposure is not expected to be significant. Therefore, an acute inhalation toxicity study was not considered necessary.

Irritation and sensitisation
The notified chemical is non-irritating to rabbit skin and did not cause skin sensitisation when tested at 5, 10 and 25% concentration. In an eye irritation study in rabbits, treated eyes showed conjunctival redness, chemosis and discharge, but all irritation symptoms resolved within 72 hours. Blue staining of the cornea and nictitating membrane was noted in treated eyes and did not fully resolve by the end of the 21-day study period. The notified chemical is considered severely irritating due to the persistence of eye colouration.

Repeated dose toxicity
The notified chemical was administered orally to rats by gavage for a period of twenty-eight consecutive days at dose levels of 30, 300 and 1000 mg/kg/day. Effects included treatment-related renal changes in male rats treated with all dose levels consistent with the well-documented condition known as hydrocarbon nephropathy. This only occurs in male rats and is not indicative of a hazard to human health. Blue fur staining and accumulations of blue pigment in several organs were observed mainly in animals treated with 300 and 1000 mg/kg/day. Most of these observations were still present after the recovery period, though were not considered adverse but to be a consequence of the coloured nature of the notified chemical. In addition, the stomach effects were observed in both sexes and at all dose levels. These effects were reversed at the end of recovery period. It was concluded by the study author that a "No Observed Effect Level" (NOEL) or a "No Observed Adverse Effect Level" (NOAEL) could not be established due to the effects observed at all dose levels. It is noted that these effects do not warrant classification of the notified chemical.

Mutagenicity
The notified chemical was not mutagenic to any bacterial strain in a bacterial reverse mutation test and was not clastogenic to Chinese hamster lung cells in an *in vitro* mammalian chromosome aberration test. The notified chemical was not clastogenic in an *in vivo* mammalian erythrocyte micronucleus test.

In an *in vitro* mammalian cell gene mutation test, the notified chemical was not mutagenic to L5178Y cells following a 4-hour exposure in the absence and presence of metabolic activation. However, the notified chemical was considered to be mutagenic to L5178Y cells following a 24-hour exposure in the absence of metabolic activation at dose levels with significant levels of notified chemical-induced toxicity.

Health hazard classification
Based on the eye irritation study, the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Xi; R41 Risk of serious damage to eyes

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the available toxicological data, the notified chemical causes transient irritation and irreversible colouration of the eyes. However, the risk of eye exposure to service technicians and office workers is extremely low given that the sealed cartridge packaging and printing process is unlikely to lead to ocular exposure to the ink. The low concentration of the notified chemical within the ink (< 5%) further reduces the risk of potential eye damage from exposure. Office staff and service technicians may experience dermal exposure when replacing spent cartridges, clearing paper jams or during maintenance and servicing, but the notified chemical is neither a skin irritant nor a skin sensitizer. In addition, direct exposure to the notified chemical is unlikely as it binds to the paper when dried. Overall, the notified chemical is not considered to pose an unreasonable risk to workers, based on the expected minimal exposure.

6.3.2. Public Health

There is potential for widespread exposure to the public through home use of printer ink containing the notified chemical (< 5%) when printing and replacing spent cartridges, similar to the exposure scenario for workers in occupational settings. Based on the relatively low proportion in the ink (< 5%), the infrequency of use and the type of packaging of the ink cartridge that minimises possible exposure, the notified chemical is not considered to pose an unreasonable risk to the public if the ink cartridges are used as intended.

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 into Australia as a component of ink in ready-to-use sealed printing cartridges for home or office inkjet printers. No manufacturing, reformulation or repackaging of the notified chemical will take place in Australia. Environmental release of the notified chemical is unlikely to occur during importation, storage and transportation as containers are designed to minimise release. In the event of an accidental spill the ink containing the notified chemical will be adsorbed with inert material and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be contained in ink cartridges and it is expected that < 1% of the annual import volume of the notified chemical may be spilt. If leakage or spillage does occur, the ink is expected to be physically contained with absorbent material and disposed of to landfill. The ink cartridges will be contained within the printer until the contents are consumed. The empty cartridges, estimated to contain < 1% of the annual import volume of notified chemical, will be removed and disposed of to landfill or sent to the manufacturer for recycling.

RELEASE OF CHEMICAL FROM DISPOSAL

Most of the notified chemical will be bound to printed paper and, once the ink has dried, will be contained in an inert matrix. It is assumed that 50% of the waste paper will end up in landfill and the rest will undergo paper recycling processes. During recycling processes, waste paper will be repulped using a variety of chemical agents which, amongst other things, enhance detachment of ink from the fibres. Due to its high water solubility, the notified chemical may partition to the supernatant water which will be released to the sewer. Notified chemical in the sludge generated during the recycling process will be sent to landfill for disposal.

7.1.2. Environmental Fate

The majority of the notified chemical will be bound to paper, of which half is assumed to be recycled. During the paper recycling process, waste paper will be repulped using a variety of alkaline, dispersing and wetting agents, water emulsifiable organic solvents and bleaches. Some of the ink in the recycled paper may partition to sludge and will therefore be disposed of to landfill. However, due to the high water solubility of the notified chemical, a greater proportion can be expected to remain in the aqueous phase released to the sewer. The notified chemical is not readily biodegradable but demonstrated inherent, primary biodegradation. The potential for bioaccumulation of the notified chemical is expected to be low in exposed aquatic organisms due to its high water solubility and low log Kow.

In landfill, notified chemical in sludge may leach due to its high water solubility and low adsorption coefficient. However, the notified chemical is likely to remain in the ink matrix bound to paper that is disposed of to landfill. The notified chemical is expected to slowly degrade through biotic and abiotic processes to form water, oxides of carbon, nitrogen, sulfur and inorganic salts.

For the details of the environmental fate studies please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

Under a worst case scenario, it was assumed that 50% of the total import volume of notified chemical would be released to sewers from paper recycling with no removal of the notified chemical by sewerage treatment plants (STPs). It was assumed the release of the notified chemical will occur over 260 days per annum into the total Australian effluent volume. This corresponds to release from recycling processes only on working days, based on a 5 day work week.

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%	
Annual quantity of chemical released to sewer	500	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	1.92	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.45	µg/L
PEC - Ocean:	0.045	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 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.454 µg/L may potentially result in a soil concentration of approximately 3.029 µg/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 15.15 µg /kg and 30.29 µg /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 (96 h) > 100 mg/L	Not harmful to fish
Daphnia Toxicity	EC50 (48 h) = 91 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	E_rC50 (72 h) > 100 mg/L	Not harmful to algae

Inhibition of Bacterial Respiration	IC50 (3 h) > 1000 mg/L	Does not inhibit microbial respiration

Under the Globally Harmonised System (GHS) of Classification and Labelling of Chemicals (United Nations, 2009) the notified chemical is classified as not acutely harmful to fish and algae and harmful to aquatic invertebrates. The notified chemical is therefore formally classified 'Acute Category 3; Harmful to aquatic life'. Based on the acute toxicity data and biodegradation studies, the notified chemical is formally classified 'Chronic Category 3; Harmful to aquatic life with long lasting effects' under the GHS.

7.2.1. Predicted No-Effect Concentration

The endpoint for the most sensitive species (daphnia) from ecotoxicological studies conducted on the notified chemical was used to calculate the Predicted No-Effect Concentration (PNEC). An assessment factor of 100 was used as acute toxicity endpoints are available for the effects of the notified chemical on aquatic species from three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Daphnia, 48 h)	91	mg/L
Assessment Factor	100	
PNEC:	910	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.45	910	4.95×10^{-4}
Q - Ocean	0.045	910	4.95×10^{-5}

The Risk Quotients (Q = PEC/PNEC) for the worst case discharge scenario have been calculated to be << 1 for the river and ocean compartments. This indicates the notified chemical is not considered to pose an unreasonable risk to the aquatic environment based on its assessed use pattern.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]:

Xi; R41 Risk of Serious Damage to Eyes

and

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2009) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Serious Eye Damage/Eye Irritation	1	Irreversible effects on the eye/serious damage to eyes
Aquatic Environment	Acute Category 3	Harmful to aquatic life
	Chronic Category 3	Harmful to aquatic life with long lasting effects

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

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

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

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- Safe Work Australia should consider the following health hazard classification for the notified chemical:

  -Xi; R41 Risk of serious damage to eyes

- Use the following risk phrases for products/mixtures containing the notified chemical:

  -Conc ≥ 10%: R41
  -5% ≤ concentration < 10%: R36

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as used in printing inks:
  - Avoid contact with eyes

- 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(2) of the Act; if
  - the function or use of the chemical has changed from dye for inkjet printer inks (< 5% concentration), or is likely to change significantly;
  - the amount of chemical being introduced has increased from 1 tonne per year, or is likely to increase, significantly;

- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the product 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 Not determined

Method EC No 440/2008 A.1 Melting/Freezing Temperature.
Remarks Differential scanning calorimetry was used. The test substance has been determined to decompose from approximately 315 ± 0.5°C. As the test substance decomposed, no value for the melting temperature could be determined.
Test Facility Harlan Laboratories Ltd (2009a)

Density 1740 kg/m^3 at 20.0 ± 0.5°C

Method EC No 440/2008 A.3 Relative Density.
Remarks A Quantachrome MVP-2 gas comparison pycnometer was used.
Test Facility Harlan Laboratories Ltd (2009a)

Vapour Pressure < 2.4 × 10^{-8} kPa at 25°C

Method EC No 440/2008 A.4 Vapour Pressure.
Remarks A vapour pressure balance was used.
Test Facility Harlan Laboratories Ltd (2009b)

Water Solubility 316 – 340 g/L at 20°C

Method EC No 440/2008 A.6 Water Solubility
Remarks Flask Method. It was not possible to prepare samples at 5 times saturation level, as recommended in the guideline, due to the formation of highly viscous samples. Hence a number of individual samples were prepared at increasing nominal concentrations and the water solubility was estimated based on visual inspection. The solubility range was taken to be from the lowest stationary concentration to the highest mobile concentration.
Test Facility Harlan Laboratories Ltd (2009a)

Hydrolysis as a Function of pH $t_{1/2}$ > 1 year at 25°C, pH 4, 7 and 9

Method EC No 440/2008 C.7 Abiotic Degradation: Hydrolysis as a Function of pH

pH	*T (°C)*	*t½*
4	25	> 1 year
7	25	> 1 year
9	25	> 1 year

Remarks HPLC method. Less than 10% hydrolysis was observed after 5 days at 50°C at pH 4, 7, and 9. Therefore, the test substance is considered stable with a half life greater than 1 year at 25°C.
Test Facility Harlan Laboratories Ltd (2009a)

Partition Coefficient (n-octanol/water) log Kow ≤ -3.17 at 21.5°C

Method EC No 440/2008 A.8 Partition Coefficient.
Remarks Shake flask method. Test was performed at pH 7. The test substance concentration in each phase was determined by HPLC.
Test Facility Harlan Laboratories Ltd (2009a)

Adsorption/Desorption log K_{oc} < 1.25 at 30°C

Method EC No 440/2008 C.19 Adsorption Coefficient
Remarks HPLC method
Test Facility Harlan Laboratories Ltd (2009a)

Particle Size 41.6% < 100 μm and 0.417% < 10 μm

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

Range (μm)	*Mass (%)*
< 100	41.6
< 10	0.417
< 5.5	0.365

Remarks The sieve method was used for screening test and the cascade impactor method was used for definitive test.
Too few particles were of a size less than 10.0 μm to allow accurate assessment of mass median aerodynamic diameter.
Test Facility Harlan Laboratories Ltd (2009a)

Flammability (solids)

Method EC No 440/2008 A.10 Flammability (Solids).
Remarks The flammability (solids) was determined by measuring the burning rate of test substance prepared as a pile of set dimensions.
In the preliminary screening test, the pile failed to ignite during the two minutes that the Bunsen flame was applied. The result of the preliminary screening test obviated the need to perform the main test.
Test Facility Harlan Laboratories Ltd (2009b)

Autoignition Temperature 358°C

Method EC No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks The test substance was heated in an oven.
Test Facility Harlan Laboratories Ltd (2009b)

Explosive Properties Predicted negative

Method EC No 440/2008 A.14 Explosive Properties.
Remarks The structure of the test substance was assessed for chemical groups that imply explosive properties.
Based on the chemical structure of the test substance the result for the explosive properties has been predicted negative.
Test Facility Harlan Laboratories Ltd (2009b)

Surface Tension 72.6 mN/m at 21.5°C

Method EC No 440/2008 A.5 Surface Tension
Remarks Concentration: 1.03 g/L
Test Facility Harlan Laboratories Ltd (2009a)

Oxidizing Properties Predicted negative

Method EC No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks The structure of the test substance was assessed for chemical groups that would imply oxidising properties.
Based on the chemical structure the result for the oxidising properties has been predicted negative.
Test Facility Harlan Laboratories Ltd (2009b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure. EC Directive No. 440/2008 B.1 bis Acute toxicity (oral) fixed dose method.
Species/Strain	Rat/Wistar
Vehicle	A suspension in arachis oil BP
Remarks - Method	No deviations from the protocol. Following a sighting test at dose levels of 300 and 2000 mg/kg bw, a further group of four fasted females was given a single dose of test substance at a dose level of 2000 mg/kg bw

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	300	0
2	1 F	2000	0
3	4 F	2000	0

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted during the observation period. Faeces stained blue was noted in all animals one and two days after dosing.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	All animals showed expected gains in bodyweight over the observation period.
CONCLUSION	The notified chemical is very of low toxicity via the oral route.
TEST FACILITY	Harlan Laboratories Ltd (2009c)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive No. 440/2008 B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 Males
Vehicle	Moistened with distilled water
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant deviations from the protocol. Only two rabbits were used for the test.

RESULTS

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

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.
STA = blue staining of the skin.

Remarks - Results	Blue staining was noted at the treatment sites of both animals throughout

the study. No evidence of skin irritation was noted during the study.
All animals showed expected gains in bodyweight during the study.

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

TEST FACILITY Harlan Laboratories Ltd (2009d)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD Evaluation of Skin Irritation Potential using the EPISKIN™ Reconstituted Human Epidermis Model
The notified chemical (10 mg) was applied to EPISKIN™ reconstituted human epidermis tissues in triplicate for an exposure period of 15 minutes. The tissues were subsequently rinsed and then incubated for approximately 42 hours. Triplicate positive (sodium dodecyl sulphate, 5%) and negative (phosphate buffered saline) controls were treated similarly. Following the incubation time, the tissues were placed on a plate shaker for 15 minutes prior to MTT ([3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)-loading. The maintenance medium from beneath each tissue was transferred to micro tubes and stored in a freezer for possible inflammatory mediator determination. After MTT loading a total biopsy of each epidermis was made and placed into micro tubes containing acidified isopropanol for extraction of formazan crystals out of the MTT-loaded tissues.
At the end of formazan extraction period each tube was mixed thoroughly and duplicate samples were used to measure the optical density at 540 nm. Data were presented in the form of % viability (MTT reduction in the test substance treated tissues relative to negative control tissues).

Vehicle None

Remarks - Method Due to the blue colour of the test substance it was not possible to determine if the test substance directly reduced MTT. Instead, killed control tissues were included in the assay to correct the results of the MTT assay if necessary. However the killed tissues demonstrated no absorbency and therefore the results of the killed tissues were not used for reporting purposes.

RESULTS

Test Material	OD_{540} of tissues	Mean OD_{540} of triplicate tissues	± SD of OD_{540}	Relative individual tissue viability %	Relative individual tissue viability %	± SD of % viability
Negative Control	0.758	0.770	0.025	98.4	100*	3.19
	0.753			97.8		
	0.798			103.6		
Positive Control	0.045	0.058	0.034	5.8	7.6	4.42
	0.033			4.3		
	0.097			12.6		
Test substance	0.803	0.790	0.011	104.3	102.6	1.48
	0.782			101.6		
	0.785			101.9		

*The mean viability of the negative control tissues is set as 100%.

Remarks - Results The relative mean viability of the test substance treated tissues was 102.6% after a 15-minute exposure.
Following the 15-minute exposure, the test substance treated tissues appeared blue which was considered indicative of viable tissue.
The relative mean tissues viability for the positive control treated tissues was ≤ 40% relative to the negative control treated tissues and the Standard

Deviation (SD) value of the % viability was ≤ 20%. The positive control acceptance criterion was therefore satisfied.
The mean OD_{540} for the negative control treated tissues was ≥ 0.6 and the SD value of the % viability was ≤ 20%. The negative control acceptance criterion was therefore satisfied.

CONCLUSION: The test substance was considered to be non-irritating to the skin.

TEST FACILITY: Harlan Laboratories Ltd (2009e)

B.4. Irritation – eye

TEST SUBSTANCE: Notified chemical (> 90% purity)

METHOD: OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive No. 440/2008 B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	1 Male
Observation Period	21 days
Remarks - Method	Due to the irreversible colouration produced in the first treated animal, no additional animals were treated.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	1s*	2s*	> 21 days	0S
Conjunctiva: chemosis	0.3	1	< 48 hours	0
Conjunctiva: discharge	0Sf	1Sf	> 21 days	0Sf
Corneal opacity	0s	0s	< 21 days	0
Iridial inflammation	0	0	0	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for the single animal.
s* = Blue staining covering the whole of the nictitating membrane (1 hr to 14 day observation)
S = Blue staining on the nictitating membrane (at 21 day observation)
Sf = Blue staining of the fur around the treated eye (at all observation times)
s = Blue staining to ¼ of the cornea (1 hr to 14 day observation)

Remarks - Results:
Blue staining of the fur around the treated eye was observed throughout the study.
Blue staining of the nictitating membrane and cornea was noted in the treated eye one hour after treatment and at all the observations until the 14-day. Blue staining of the nictitating membrane was also present at the 21-day observation. The staining did not affect evaluation of ocular effects but was considered to be irreversible.
No corneal or iridial effects were observed during the study, aside from the corneal staining noted above.
Some conjunctival irritation was noted in the treated eye from one hour to 48-hours.
No ocular effects were noted at the 72-hour and subsequent observations, aside from the blue staining.
The animal showed expected gain in bodyweight during the study.

CONCLUSION: The notified chemical is severely irritating to the eye due to irreversible colouration.

TEST FACILITY: Harlan Laboratories Ltd (2009f)

B.5. Irritation – eye

TEST SUBSTANCE: Notified chemical (> 90% purity)

METHOD: Determination of Ocular Irritation Potential Using the SkinEthic Reconstituted Human Corneal Epithelium Model
The notified chemical (30 mg) was applied to SkinEthic reconstituted human corneal epithelium tissues in triplicate for an exposure period of 10 minutes. The tissues were subsequently rinsed and then taken for MTT-loading. The remaining tissues were retained for possible histopathology. Following MTT loading the reduced MTT was extracted from the tissues. Triplicate positive (sodium dodecyl sulphate, 1%) and negative controls were treated similarly.
After extraction the absorbency of triplicate aliquots of the extracted MTT solution for each SkinEthic tissue was measured for the optical density at 540 nm. Data were presented in the form of % viability (MTT conversion relative to negative controls).

Vehicle: None

Remarks - Method: The test substance was not able to directly reduce MTT ([3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).
Due to the blue colour of the test substance it was not possible to determine if the test substance directly reduced MTT ([3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Instead, killed control tissues were included in the assay to correct the results of the MTT assay if necessary. However the killed tissues demonstrated no absorbency and therefore the results of the killed tissues were not used for reporting purposes.

RESULTS

Substance	Mean Tissue Viability	Mean OD_{540}	% Viability
Negative Control	0.907 0.966	0.937	100*
Positive Control	0.809 0.733	0.771	82.3
Test Substance	0.932 1.018	0.975	104.1

*The mean viability of the negative control tissues is set as 100%.

Remarks - Results: The relative mean viability of the test substance treated tissues after a 10-minute exposure was 104.1%.
Tissues treated with the test substance and negative controls were considered to be viable. The tissues treated with the positive control were considered to be semi-viable.

CONCLUSION: The test substance was considered to be non-irritating to the eyes.

TEST FACILITY: Harlan Laboratories Ltd (2009g)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE: Notified chemical (> 90% purity)

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 440/2008 B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse/CBA/CaOlaHsd (female)

Vehicle: 1% pluronic L 92 in distilled water

Remarks - Method: No deviations from the protocol.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	881.46 (±425.60)	1
5%	982.84 (±184.30)	1.12
10%	865.27 (±241.33)	0.98
25%	1022.40 (±494.04)	1.16
Positive Control (2,4-Dinitrobenzenesulfonic acid, sodium salt)		
10%	-	13.71

Remarks - Results: There were no deaths. No signs of systemic toxicity were noted. Blue staining on the ears and fur was noted, in animals treated with the test substance at a concentration of 25% after dosing on days 1 to 3.
Body weight changes of the test animals were comparable to control animals.

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY: Harlan Laboratories Ltd (2009h)

B.7. Repeat dose toxicity

TEST SUBSTANCE: Notified chemical (> 90% purity)

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: Rats/Wistar Han:HsdRccHan:WIST
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: No deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	30	0
mid dose	5 per sex	300	0
high dose	5 per sex	1000	0
control recovery	5 per sex	0	0
high dose recovery	5 per sex	1000	0

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

Clinical Observations
No toxicologically significant clinical signs were detected throughout the treatment period or during treatment free period.
Generalised blue staining due to the test substance was evident in animals of either sex treated with 1000 mg/kg/day throughout the treatment period and were considered to be of no toxicological importance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No toxicologically significant effects were detected in the haematological parameters, blood chemical parameters or urinalytical parameters measured.

Blue coloured urine due to the test substance was evident in animals of either sex treated with 1000 mg/kg/day and in males treated with 300 mg/kg/day and were considered to be of no toxicological importance.

Effects in Organs

Organ weights

There were no toxicologically significant changes in the organ weights measured.

Necropsy

No toxicologically significant macroscopic abnormalities were detected. Blue staining of many tissues was observed in animals treated with 300 and 1000 mg/kg/day, including at the end of recovery period. The staining was not considered to be toxicologically significant.

Histopathology

The following treatment-related changes were observed:

Stomach: A greater incidence and generally higher grades of severity of agglomeration of secretion in the mucosa, particularly adjacent to the limiting ridge, mucous cell hypertrophy/hyperplasia, higher grades of severity of submucosal inflammatory cells, and vacuolation/acanthosis/hyperkeratosis of the epithelium of the limiting ridge were seen in relation to treatment for animals of either sex treated with 1000 mg/kg/day. Mucous cell hypertrophy/hyperplasia and vacuolation/acanthosis/hyperkeratosis of the limiting ridge epithelium were also seen occasionally among animals of either sex treated with 300 mg/kg/day or at 30 mg/kg/day.

Treatment related conditions were observed to have regressed among recovery 1000 mg/kg/day animals of either sex following an additional fourteen days without treatment.

Intestinal tract: Accumulations of blue pigment were seen in the lamina propria or lymphoid tissue of the ileum and caecum of animals of either sex treated with 1000 mg/kg/day, but not at any other dose level. The colon of males at this dose level was similarly affected but to a lesser extent and not further evaluated at lower dose levels. Pigment accumulations were considered to be the test substance and there were no associated degenerative or inflammatory changes.

There was no evidence of regression of the condition among recovery 1000 mg/kg/day animals following completion of the recovery period.

Mesenteric lymph node: Accumulations of blue pigment, considered to be the test substance, were seen in animals of either sex treated with 1000 mg/kg/day. There were no associated degenerative or inflammatory changes. Animals from the remaining treatment levels were not similarly affected.

There was no evidence of regression of the condition among recovery 1000 mg/kg/day animals following an additional fourteen days without treatment and grades of severity of blue pigment accumulation were generally higher than non-recovery animals treated at 1000 mg/kg/day.

Kidneys: Accumulations of blue pigment, considered to be test substance, were seen in the renal proximal tubular epithelium of animals of either sex treated with 1000 or 300 mg/kg/day but not 30 mg/kg/day. There were no associated degenerative or inflammatory changes although associated karyomegaly was seen for one female treated with 1000 mg/kg/day.

There was no evidence of regression of blue pigment accumulation among recovery 1000 mg/kg/day animals of either sex following completion of the recovery period, with grades of severity of the condition being generally higher than those among non-recovery 1000 mg/kg/day animals of either sex with two associated instances of karyomegaly.

A higher incidence of globular accumulations of eosinophilic material was also observed in the tubular epithelium of males treated with 1000, 300 or 30 mg/kg/day. This finding is consistent with the presence of hydrocarbon nephropathy, which results from the excessive accumulation of α_2-microglobulin in renal proximal tubular epithelial cells. α_2-Microglobulin is found only in the proximal tubular epithelium of adult male rats.

There was no difference in the incidence or general severity of globular accumulations of eosinophilic material in renal proximal tubular epithelial cells between recovery control animals and recovery 1000 mg/kg/day males.

Remarks – Results

The visible signs of blue fur staining were detected in animals of either sex treated with 1000 mg/kg/day during the study (confirmed as coloured urine following urinalytical investigations). Such observations are often reported following administration of a coloured test substance or excretion of coloured metabolites. This simply represents normal excretion of the coloured compound followed by normal grooming behaviour and subsequent dispersal of the substance onto the external body surface. Such observations do not, therefore, represent systemic toxicity.

Histopathological examination revealed changes in the stomach. These were identified as a greater evidence

and generally higher grades of severity of agglomeration of secretion in the mucosa, more especially adjacent to the limiting ridge, mucous cell hypertrophy/hyperplasia, higher grades of severity of submucosal inflammatory cells and vacuolation/acanthosis/hyperkeratosis of the epithelium of the limiting ridge in animals of either sex treated with 1000 mg/kg/day. Mucous cell hypertrophy/hyperplasia and vacuolation/acanthosis/hyperkeratosis of the limiting ridge epithelium were also seen in animals of either sex treated with 300 and 30 mg/kg/day. Treatment-related conditions were observed to have regressed among recovery 1000 mg/kg/day animals following an additional fourteen days without treatment.

Accumulations of blue pigment were seen in the intestinal tract, mesenteric lymph nodes and kidneys of animals of either sex treated with 1000 mg/kg/day and in the kidneys of 300 mg/kg/day animals. There were no associated degenerative or inflammatory changes and although there was no evidence regression in recovery animals following fourteen days without treatment the effects detected were not considered to be adverse.

Further microscopic abnormalities were detected in the kidneys. A higher incidence of globular accumulations of eosinophilic material was also observed in the tubular epithelium of males treated with 1000, 300 and 30 mg/kg/day. Accumulations of globular eosinophilic material in the tubular epithelium is a well documented effect, peculiar to the male rat, which occurs in response to treatment with certain hydrocarbons. Female rats and other species do not develop "hydrocarbon nephropathy" and for this reason, the effect is not indicative of hazard to human health.

CONCLUSION
The oral administration of the test substance to rats by gavage for a period of twenty-eight consecutive days at dose levels of 30, 300 and 1000 mg/kg/day resulted in treatment related effects in animals of either sex at all dose levels, particularly effects in the stomach. A "No Observed Effect Level" (NOEL) or a "No Observed Adverse Effect Level" (NOAEL) was therefore not established.

TEST FACILITY Harlan Laboratories Ltd (2009i)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test.
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix was prepared from the livers of phenobarbital/5,6-benzoflvone induced male Sprague-Dawley rats.
Concentration Range in Main Test	a) With metabolic activation: 0, 313, 625, 1250, 2500 and 5000 µg/plate b) Without metabolic activation: 0, 313, 625, 1250, 2500 and 5000 µg/plate
Vehicle	Water
Remarks - Method	No significant deviations from the protocol.

RESULTS

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

Remarks - Results In the dose-finding test and main test, neither an increase in the number of revertant colonies (more than twice as many as that of the negative control) nor a dose-related response was observed at any doses in any strains of base-pair substitution type of frame-shift type, with or without metabolic activation.

The revenant colonies of the positive controls showed an increase of more than twice that of the negative controls and they were within limit of controls (means ± 3SD) in background data, indicating that this study was performed correctly.
The growth inhibition of the test strains by the test substance was not observed, and the precipitate on the plates was not observed either with or without metabolic activation.
In the sterility test on the test solution and the S9 mix, no growth of bacteria was observed.

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

TEST FACILITY BML, INC (2009)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line	Chinese Hamster Lung (CHL/IU) cells
Metabolic Activation System	S9 mix was prepared from the livers of phenobarbital/β-naphthoflavone induced male Han Wistar rats.
Vehicle	Eagle's Minimal Essential Medium (MEM)
Remarks - Method	No deviations from the protocol.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*,156.25,312.5*,625*,937.5*,1250*,2500	6	24
Test 2	0*, 39.06, 78.13*, 156.25*, 234.38, 312.5*, 625	24	24
Present			
Test 1	0*, 312.5*, 625*, 1250*, 2500*, 3750, 5000	6	24

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 1250	≥ 1250	> 1250	Negative
Test 2	≥ 312.5	> 312.5	> 312.5	Negative
Present				
Test 1	> 5000	> 2500	> 2500	Negative

Remarks - Results Both of the vehicle control groups had frequencies of cells with chromosome aberrations within the expected range. The positive controls induced statistically significant increases in the frequency of cells with aberrations. This confirmed the validity of the metabolising system and the test method.
The test substance did not induce any statistically significant increases in the frequency of cells with aberrations in the presence or absence of metabolic activation in any exposure group.
The test substance did not induce any statistically significant increases in the number of polyploidy cells at any dose level in any exposure group.

CONCLUSION The notified chemical was not clastogenic to CHL cells treated in vitro

under the conditions of the test.

TEST FACILITY Harlan Laboratories Ltd (2009j)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.
EC Directive 440/2008 B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test.

Cell Type/Cell Line L5178Y TK+/- 3.7.2c mouse lymphoma cell line

Metabolic Activation System S9 mix was prepared from the livers of phenobarbital/β-naphthoflavone induced male Wistar Han rats.

Vehicle R0 medium

Remarks - Method Initially one main experiment was performed. In this main experiment, L5178Y TK +/- 3.7.2c mouse lymphoma cells (heterozygous at the thymidine kinase locus) were treated with the test substance at six dose levels, in duplicate, together with vehicle (R0 medium) and positive controls. The exposure groups used were as follows: 4-hour exposures both with and without metabolic activation, and 24 hours without metabolic activation. However, a confirmatory experiment (Test 3) was performed due to the statistically significant response observed in the 24-hour exposure group in the absence of metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0, 156.25, 312.5, 625, 1250, 2500 and 5000	4 hours	48 hours	10-14 days
Test 2	0, 156.25, 312.5, 625, 1250, 2500 and 5000	24 hours	48 hours	10-14 days
Test 3	0, 625, 1250, 1875, 2500, 3750 and 5000	24 hours	48 hours	10-14 days
Present				
Test 1	0, 156.25, 312.5, 625, 1250, 2500 and 5000	4 hours	48 hours	10-14 days

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	≥ 156.25	Negative
Test 2	> 2500	≥ 2500	≥ 156.25	Positive
Test 3	-	≥ 1875	≥ 625	Positive
Present				
Test 1	> 5000	> 5000	≥ 156.25	Negative

Remarks - Results The vehicle (solvent) controls had acceptable mutant frequency values that were within the normal range for the L5178Y cell line at the TK +/- locus. The positive controls induced marked increases in the mutant frequency confirming the satisfactory performance of the test and the metabolic system.
The test substance did not induce any statistically significant or dose-related increases in the mutant frequency at the TK +/- locus in L5178Y cells in the 4-hour exposure groups in the absence and presence of metabolic activation. However, the test substance induced reproducible statistically significant and dose-related increases in mutant frequency at dose levels where significant toxicity was observed in the 24-hour

exposure groups in the absence of metabolic activation. The increases in mutant frequency were partly due to small colony formation, suggesting clastogenic activity resulting in structural chromosome damage.

CONCLUSION The test substance was considered to be mutagenic to L5178Y cells following a 24-hour exposure in the absence of metabolic activation at dose levels with significant levels of test substance-induced toxicity under the conditions of the test.

TEST FACILITY Harlan Laboratories Ltd (2009k)

B.11. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 440/2008 B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.

Species/Strain Mice/albino Hsd: ICR (CD-1)
Route of Administration Intraperitoneal route
Vehicle Distilled water
Remarks - Method No deviations from the protocol. A range-finding test was performed to find suitable dose levels of the test substance, route of administration and to investigate to see if there was a marked difference in toxic response between the sexes. There was no marked difference in toxicity of the test substance between the sexes; therefore the main test was performed using only male mice.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	7 M	0	24
			48
II (low dose)	7 M	50	24
III (mid dose)	7 M	100	24
IV (high dose)	7 M	200	24
			48
V (positive control, CP) (oral dosing)	5 M	50	24

CP=cyclophosphamide

RESULTS

Doses Producing Toxicity There were no premature deaths seen in any of the dose groups. Clinical signs were observed in animals treated with the test substance at all dose levels and exposure times. These included: hunched posture, blue staining of the anogenital area, fur stained blue, extremities blue in colour, faeces stained blue and urine strained blue.

Genotoxic Effects A small though statistically significant decrease in the PCE/NCE ratio was observed in the 24-hour 200 mg/kg test substance dose group when compared to the controls. Together with the observation of clinical signs in both the 24 and 48-hour test substance dose groups, this decrease was taken to indicate that systemic absorption had occurred and exposure to the target tissue had been achieved.
There was no statistically significant increase in the frequency of micronucleated PCE in the 48-hour 200 mg/kg test substance dose group. Very modest but statistically significant increases in the frequency of micronucleated PCE were observed in the 24-hour 100 and 50 mg/kg dose groups. However, there was no evidence of a statistically significant increase in the 24-hour 200 mg/kg dose group, the group means of micronucleated PCE were within the acceptable range for vehicle controls, and the statistical significance was considered to be due to the comparison

	to the very low concurrent vehicle control group mean. Therefore, the responses were considered to be of no toxicological significance. The positive control group showed a marked increase in the incidence of micronucleated polychromatic erythrocytes as expected. The test substance was found not to produce a toxicologically significant increase in the frequency of micronuclei in polychromatic erythrocytes of mice under the conditions of the test.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo micronucleus test in the mouse.
TEST FACILITY	Harlan Laboratories Ltd (2009l)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability (study 1)

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test
Inoculum	Activated sewage sludge from domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	TOC analyser
Remarks - Method	The test was conducted for 28 days in accordance with the above guidelines. In an initial test conducted with the test substance at 10 mg C/L, inhibition of the sewage sludge microorganisms was observed and hence the definitive test was carried out at 5 mg C/L. The test substance was added to a liquid medium inoculated with sewage microorganisms and aerated with CO_2-free air at approximately 21°C. CO_2 production was analysed. On day 28, 1 mL of concentrated HCl was added to each vessel to drive off any dissolved CO_2 present. The vessels were resealed, aerated overnight and the final sample was taken from both vessels on Day 29. A reference (sodium benzoate), and toxicity control were run in parallel.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
8	5	8	80
14	0	14	96
28	13	28	102
29	19	29	100

Remarks - Results	All validity criteria were satisfied. The reference compound reached the 60% pass level by day 14 indicating the suitability of the inoculum. The toxicity control attained 55% degradation after 14 days indicating the notified chemical is not toxic to the inoculum. The test substance was found to be biodegradable (19%) under the conditions of the test. However, as biodegradation did not reach the pass level of > 60% CO_2 production within the 10 day window, it cannot be classed as readily biodegradable.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Harlan Laboratories Ltd (2009m)

C.1.2. Ready biodegradability (study 2)

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from domestic sewage plant
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	BOD
Remarks - Method	No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0.0	1	0.0
7	1.5	7	71.7
14	3.0	14	82.8
28	4.5	28	87.2

Remarks - Results: All validity criteria were satisfied. The reference compound (aniline) reached the 60% pass level by day 14 indicating the suitability of the inoculum. The toxicity control attained 62.8% degradation after 14 days indicating the notified chemical is not toxic to the inoculum.

CONCLUSION: The notified chemical is not readily biodegradable.

TEST FACILITY: Supervision and Test Center for Pesticide Safety Evaluation and Quality Control (2010a)

C.1.3. Inherent biodegradability

TEST SUBSTANCE: Notified chemical (> 90% purity)

METHOD: OECD TG 302 C Inherent Biodegradability: Modified MITI Test (II)
- Inoculum: Sludge from ten sites (sewage treatment plants, rivers, lakes)
- Exposure Period: 28 days
- Auxiliary Solvent: Not reported
- Analytical Monitoring: BOD
- Remarks - Method: No significant deviations were reported.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
1	4.9	1	2.9
7	8.7	7	80.2
14	15.2	14	86.9
28	24.4	28	88.1

Remarks - Results: Degradation of the reference compound (aniline) exceeded 75% after 7 days thus verifying the activity of the inoculum and validating the test.

CONCLUSION: The notified chemical met the criteria for inherent and primary biodegradability

TEST FACILITY: Supervision and Test Center for Pesticide Safety Evaluation and Quality Control (2010b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish (study 1)

TEST SUBSTANCE: Notified chemical (> 90% purity)

METHOD: OECD TG 203 Fish, Acute Toxicity Test – Semi static
EC No 440/2008 C.1 Fish, Acute Toxicity Test – Semi static
- Species: Rainbow trout (*Oncorhynchus mykiss*)
- Exposure Period: 96 hours
- Auxiliary Solvent: None reported
- Water Hardness: 140 mg $CaCO_3$/L
- Analytical Monitoring: UV/Vis

Remarks – Method	Following a range finding test, a limit test was conducted at 100 mg/L under semi static conditions for a period of 96 h according to the guidelines above. Test conditions were: 14°C, pH 7.5 – 7.8, 86 – 131% ASV O_2, 12 hours dark and 12 hours light period.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*				
Nominal	*Actual (at 96 h)*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	< LOQ	7	0	0	0	0	0
100	92.45*	7 × 2	0	0	0	1	1

LOQ = 1.1 mg/L *Mean of two replicates.

LC50	> 100 mg/L at 96 hours (based on nominal concentration)
NOEC	100 mg/L at 96 hours (based on nominal concentration)
Remarks – Results	All validity criteria for the test were satisfied and no significant deviations were reported. Staining of the fins, mouth and body was observed on the fish. However, this was not considered to be a sub-lethal effect of exposure. A single mortality was observed at 72 h and was considered to be due to natural causes and/or handling stress.

CONCLUSION The notified chemical is not harmful to fish

TEST FACILITY Harlan Laboratories Ltd (2009n)

C.2.2. Acute toxicity to fish (study 2)

TEST SUBSTANCE Notified chemical (> 90% purity)

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi static

Species	Zebra fish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None reported
Water Hardness	126 mg $CaCO_3$/L
Analytical Monitoring	UV/Vis
Remarks – Method	Following a range finding test, a limit test was conducted at 100 mg/L under semi static conditions for a period of 96 h according to the guidelines above. The controls were kept in dilution water. Test conditions were: 21.8 – 22.3°C, pH 7.07 – 7.67, ≥ 60% ASV O_2, 12 hours dark and 12 hours light period.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*				
Nominal	*Actual**		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	< LOQ	10	0	0	0	0	0
100	92.0	10	0	0	0	0	0

LOQ = 2.4 mg/L. *Geometric mean of fresh and expired solutions at 24, 72 and 96 h.

LC50	> 100 mg/L at 96 hours (based on nominal concentration)
NOEC	100 mg/L at 96 hours (based on nominal concentration)
Remarks – Results	All validity criteria for the test were satisfied and no significant deviations were reported. No mortalities or toxic signs were observed.

CONCLUSION The notified chemical is not harmful to fish

TEST FACILITY Supervision and Test Center for Pesticide Safety Evaluation and Quality Control (2010c)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test - Static EC No 440/2008 C.2 *Daphnia* sp, Acute Immobilisation Test - Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	~250 mg $CaCO_3$/L
Analytical Monitoring	UV/Vis
Remarks - Method	Following a range-finding and limit test, a definitive test was conducted in accordance with the guidelines above. No significant deviations to protocol were reported. Test conditions were: 20 – 21°C, pH 7.8 – 8.1, 8.3 – 9.2 mg O_2/L. A positive control was run with potassium dichromate. The EC50 value at 48 h and the slope of the response curve and its standard error were calculated by the maximum-likelihood probit method.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Number Immobilised*	
Nominal	*Actual at 48 h*		*24 h*	*48 h*
Control	< LOQ	10 × 2	0	0
10	8.74	10 × 2	0	0
18	16.3	10 × 2	0	3
32	28.7	10 × 2	0	0
56	49.4	10 × 2	0	9
100	92.4	10 × 2	0	10

LOQ = 0.11 mg/L

EC50	91 mg/L at 48 hours (based on nominal concentrations)
NOEC	32 mg/L at 48 hours (based on nominal concentrations)
Remarks - Results	All validity criteria for the test were satisfied. The results from the positive control was EC50 = 0.71 mg/L at 48 hours, which was in the normal range for the reference material. Immobilisation of 3 daphnids was observed at 18 mg/L at 48 h, however this was considered to be caused by natural handling and/or handling stress. Hence the NOEC was considered by the study authors to be 32 mg/L where no immobilisation was observed.
CONCLUSION	The notified chemical is harmful to aquatic invertebrates
TEST FACILITY	Harlan Laboratories Ltd (2009o)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical (> 90% purity)
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC No 440/2008 C.3 Freshwater Alga and Cyanobacteria, Growth Inhibition Test
Species	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0, 100 mg/L Actual: < LOQ (1.1 mg/L), 90.95 mg/L (at 72 h) (mean of two measurements for pooled replicates).
Auxiliary Solvent	None reported
Water Hardness	0.15 mmol Ca^{2+} and Mg^{2+}
Analytical Monitoring	UV/Vis
Remarks - Method	Following a range finding test, a limit test at 100 mg/L was conducted in

accordance with the guidelines above. A positive control with potassium dichromate was run under similar exposure conditions to the limit test. Due to the coloured nature of test solutions, the method was modified to have increased light intensity and decreased test volume. This is recommended (EC, 2006) to minimise the effects of light adsorption by the test substance at the wavelengths required for photosynthetic growth. Test conditions were: 24 ± 1°C, pH 7.2 – 7.7, constant illumination at 10,000 lux and shaking. NOECs were estimated by Student's t-test incorporating Bartlett's test for homogeneity of variance. EC50s were estimated by inspection of the growth rate data and yield data.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 100	100	> 100	100

Remarks - Results

All validity criteria were satisfied. Results from the positive control were within normal range for the reference material.

Spectrophotometer measurements taken at the wavelength required for photosynthesis (460 and 665 nm) showed that the most significant absorption of the test solutions occurred at 460 nm at both 20 and 200 mg/L. Modifications to the guidelines above to increase the light intensity and decrease the sample volume overcame this absorption effect, resulting in no significant effect on algal cells.

The reported toxicity endpoints were based on nominal concentrations since the measured concentrations were within ±20% of nominal values.

CONCLUSION

The notified chemical is not harmful to algae

TEST FACILITY

Harlan Laboratories (2009p)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE

Notified chemical (> 90% purity)

METHOD

OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC No 440/2008 C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum: Activated sewage sludge
Exposure Period: 3 hours
Concentration Range: Nominal: 10, 32, 100, 320 and 1000 mg/L
Actual: Not reported
Remarks – Method: After a range finding test, the definitive test was conducted according to the guidelines above at test substance concentrations of 10 - 1000 mg/L dispersed in dechlorinated tap water with the addition of a synthetic sewage as a respiratory substrate. A blank control and reference (3,5-dichlorophenol) control were run in parallel.

The rate of respiration was determined after 3 h contact time and compared to the results from the control and reference material. Test conditions: approximately 21°C, pH 7.4 – 7.6.

RESULTS

IC50 (3 h): > 1000 mg/L
NOEC (3 h): 1000 mg/L
Remarks – Results: All validity criteria for the test were satisfied and no significant protocol

	deviations were reported.
CONCLUSION	The notified chemical does not inhibit the respiration of waste-water microorganisms
TEST FACILITY	Harlan Laboratories Ltd (2009q)

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