File No: STD/1375

November 2010

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Magenta Pigment in Digital Printing Press Ink

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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Magenta Pigment in Digital Printing Press Ink

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Hewlett Packard Australia Pty Ltd (ABN: 74 004 394 763)
353 Burwood Highway
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, impurities, use details, import volume

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
United States, Canada, European Union, China, Japan, Korea

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Magenta Pigment in Digital Printing Press Ink

MOLECULAR WEIGHT
< 500 Da

ANALYTICAL DATA
Reference NMR, IR, HPLC, UV/vis and mass spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight) None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Pink powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	> 400°C at 101.3 kPa	Measured
Density	1421 kg/m^3 at 19.3°C	Measured
Vapour Pressure	8.36 x 10^{-14} kPa at 25°C	Calculated
Water Solubility	Not determined	Based on structural considerations, the water solubility is expected to be very low.
Hydrolysis as a Function of pH	Not determined	Not expected at environmental pH range (4 - 9).

Partition Coefficient (n-octanol/water)	Not determined	Due to the limited solubility in water and structural considerations, expected to partition to the octanol phase.
Surface Tension	67.9 mN/m at 20.7 °C	Measured
Adsorption/Desorption	Not determined	Due to the low solubility in water, it is expected to partition to soil and sediment.
Dissociation Constant	Not determined	Does not contain structural elements that are capable of dissociation.
Particle Size	Inhalable fraction (<100 μm): 100% Respirable fraction (<10 μm): 99.82% MMD* = 1.2 μm; range 0.3 – 40 μm	Measured
Flash Point	Not determined	High melting point solid
Flammability	Not highly flammable	Measured
Autoignition Temperature	316°C	Measured
Explosive Properties	Not explosive	Expert statement
Oxidising Properties	Non-oxidising	Expert statement

* MMD = Mass Median Diameter

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

Reactivity
The notified chemical is considered to be stable under normal conditions of use. Typical decomposition products are oxides of carbon and nitrogen.

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 component of finished liquid ink products at concentrations up to 5%.

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, Melbourne

IDENTITY OF RECIPIENTS
Hewlett Packard Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The ink containing the notified chemical will be imported by sea in 205 L lined steel drums. It will then be transported by road to the notifier's warehouse and subsequently to printing facilities.

USE

The notified chemical will be used as a component of inks used in industrial digital inkjet printing. It will be used to print books, newsprint, etc.

OPERATION DESCRIPTION
Ink containing the notified chemical at concentrations up to 5% will be pumped (using a high pressure pump) directly from the import drums to the printheads of the printing machine. It will then be printed onto the material or pass into a collection gutter for re-use. Following printing, the ink will be over-coated with a fixer ink and then air dried onto the surface of the material prior to exiting the printer.

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)*
Transport and storage	10 - 20	4 - 8	50
Service technicians	6	0.5 - 6	25 (maximum)
Printer operators	> 20	8 - 10	210 (maximum)

EXPOSURE DETAILS
The fully automated nature of the printing process is expected to minimise worker contact with the notified chemical (up to 5% concentration). However, worker exposure to the notified chemical, mainly via the dermal route, may occur during certain parts of the printing process.

Dermal exposure of workers to the notified chemical (< 5%) may occur during the manual connection of the ink drums to the printing machine. Workers may wear gloves during such operations, thus acting to lower exposure.

Dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (< 5%) may occur during the manual process of replacing ink drums. Such exposure is expected to be minimised by the wearing of gloves and goggles and the use of local exhaust ventilation.

Dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (< 5%) may occur during monitoring of the operation of the printing machines (such as clearing jams, etc), as well as during equipment maintenance and servicing. Exposure is expected to be lowered by the wearing of coveralls, goggles, gloves and respirators/dust masks.

Dermal exposure of workers to the notified chemical (< 5%) may occur when handling materials that have been printed with inks containing the notified chemical. Such exposure is expected to be minimal as the materials will only exit the printer after they are dried and have been coated with a fixer ink and thus there is limited potential for release of the notified chemical.

6.1.2. Public exposure
Ink products containing the notified chemical will not be sold to the public. Members of the public may make contact with materials that have been printed with inks containing the notified chemical, however, on such materials the notified chemical is dried and expected to remain bound to the substrate print matrix. Thus public exposure to the notified chemical is expected to be negligible.

6.2. Human health effects assessment

The results from toxicological investigations conducted on a mixture containing the notified chemical and two structurally related chemicals are summarised in the table below. Details of these studies can be found in Appendix B (with the exception of the acute oral toxicity study).
The toxicity of the mixture is expected to closely estimate the toxicological properties of the notified chemical itself.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation (up to 10% concentration)
Rat, repeat dose oral toxicity – 28 days.	NOAEL 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution.
The notified chemical is not expected to be significantly absorbed dermally or from the gastrointestinal tract due to its low water solubility. Inhalation of the powder form of the notified chemical is expected to result in uptake and accumulation in the respiratory tract. Note that the powder form of the notified chemical will not be available in Australia.

Acute toxicity.
The notified chemical was found to be of low acute oral toxicity with a LD50 > 2000 mg/kg bw (tested using 6 animals). No mortalities or signs of systemic toxicity were observed. Some animals displayed dark red faeces on days 2 to 3 or 2 to 6. The treated animals displayed expected weight gains during the study (RCC, 2004g).

The notified chemical was also of low acute dermal toxicity with a LD50 > 2000 mg/kg bw.

Irritation and Sensitisation.
The notified chemical was a slight skin and eye irritant in rabbits. It was not a skin sensitiser when tested in a mouse local lymph node assay (LLNA).

Repeated Dose Toxicity
A 28-day repeat dose oral toxicity study in rats established an NOAEL of 1,000 mg/kg bw/day for the notified chemical. Administration at this dosage level did not result in mortality or any effects considered to be of toxicological significance.

Mutagenicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic in a chromosome aberration test in Chinese hamster V79 lung cells.

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

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
The notified chemical was found to be a slight skin and eye irritant. Workers will handle the notified chemical at maximum concentrations of 5%. At such concentrations, irritancy effects are not expected. In addition, measures will be in place during handling in order to lower the potential for exposure (dermal, ocular and inhalation), such as automated processes and the use of personal protective equipment.

It is also noted that the notified chemical will not be introduced or used in Australia in a powder formulation and/or at 100% and thus inhalation of particles of respirable size will not occur. Inhalation of aerosols containing the notified chemical may occur, though this potential is expected to be reduced due to the control measures stated above.

In summary, the risk to workers associated with handling of the notified chemical is not considered to be unacceptable under the conditions described.

6.3.2. Public health

The inks containing the notified chemical at up to 5% will not be sold to the public. No exposure is expected from the dried printed materials as it will be covered with an additional layer. Therefore, risk to the public from the notified chemical is not expected.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

No release is expected as manufacturing and reformulation of the ink containing the notified chemical will not take place in Australia. Environmental release of the notified chemical is limited during importation, storage and transportation. Spillage during a transport accident is the most likely reason for environmental release. It is estimated that a maximum of 1% of the imported ink and hence the notified chemical may be released as a result of spills and leaks, which should be disposed of to landfill although some may be disposed to the sewer.

RELEASE OF CHEMICAL FROM USE

The notified chemical in digital printing press ink will be applied to paper by electrostatic deflection plates and the print will be protected with a fixer ink which is air dried. Only a small fraction of the notified chemical is used to print and the majority is recycled. A maximum of 2% notified chemical from equipment cleaning waste will be disposed by contractors to landfill. A further 1% notified chemical is expected to be released from spills which should be collected for disposal to landfill but some may be released to the sewer. The notified chemical will be bound within an inert matrix on the printed end-use articles during the printing process.

RELEASE OF CHEMICAL FROM DISPOSAL

Most of the notified chemical applied via printing processes will share the fate of the paper, which may be either sent to landfill or recycled. It is assumed that 50% of the paper will end up in landfill and the other 50% will undergo paper recycling processes. During this process, waste paper will be repulped using a variety of chemical agents which, amongst other things, enhance detachment of inks from the fibres.

Considering the very low water solubility, residues of the notified chemical that are removed during paper recycling are expected to partition to sludge. Formulation wastes (a minor amount) will be collected and disposed of to landfill and sewer. Waste paper and sludge from paper recycling is expected to be disposed of to landfill and the sludge may be used for soil remediation.

7.1.2 Environmental fate

No environmental fate data and studies were provided. The notified chemical is practically insoluble in water and has relatively low vapour pressure. The notified chemical is expected to partition to soils and sediment due to its very low water solubility. The notified chemical is not expected to be readily biodegradable. Due to its very low aquatic exposure, bioaccumulation is not expected. In landfill, when used for soil remediation the notified chemical is not expected to be mobile based on its low water solubility and the residue is expected to undergo slow degradation by biotic and abiotic processes to water and oxides of carbon and nitrogen.

7.1.3 Predicted Environmental Concentration (PEC)

The following Predicted Environmental Concentration assumes 50% recycling of printed paper and as a worst case scenario assumes no recovery within STPs.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	< 1000	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	200.0	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:	0.05	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.

One assumption is that, based on the expected very low water solubility of the notified chemical, all of it partitions to the sludge. Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 4.544 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.03 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated biosolids application, the concentration of notified chemical in the applied soil in 5 and 10 years may approximate 0.15 mg/kg and 0.3 mg/kg, respectively.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the ink mixture containing 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 (96 hour)	LC50 > limit of water solubility	Not harmful to fish
Daphnia Toxicity (48 hour)	EC50 > limit of water solubility	Not harmful to aquatic invertebrates
Algal Toxicity (72 hour) for Study 1	EC50 > limit of water solubility	Not harmful to algae
Algal Toxicity (72 hour) for Study 2	EC50 > limit of water solubility	Not harmful to algae

The test substance used for the above studies contained the notified chemical and two analogous chemicals. The test substance, and by inference the notified chemical, is not acutely harmful to fish, aquatic invertebrates, and algae up to its limit of solubility in water. In reality, the notified chemical does not show effects to aquatic life at its saturation level in the medium. The notified chemical is not expected to be chronically toxic to aquatic life based on the results of the algal studies. Classification should only be based on toxic responses observed in the soluble range, therefore, the notified chemical is not formally classified for acute hazard under the Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2009). The notified chemical is not classified for chronic hazards to the aquatic environment.

7.2.1 Predicted No-Effect Concentration

A PNEC was not calculated since the notified chemical is not harmful to aquatic organisms up to its limit of solubility in water.

7.3. Environmental risk assessment

The notified chemical is not expected to pose an unacceptable risk to the aquatic environment since it is not harmful to aquatic organisms up to its limit of solubility in water and there is expected to be very low aquatic exposure based on its very low solubility in water.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the data provided, the notified chemical is not classified as hazardous according to 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 reported use pattern, the notified chemical is not considered to pose a risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Local exhaust ventilation

- 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 notified chemical is introduced in powder form;

or

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from component of liquid inks used in industrial digital inkjet printing at 5%, or is likely to change significantly;
- the amount of chemical being introduced has increased from 1 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 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

* = test substance consisting of the notified chemical with two other structurally related chemicals.

Melting Point/Freezing Point* > 400°C at 101.3 kPa

Method OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks The test substance was not observed to melt under the conditions of the test.
Test Facility RCC (2004a)

Density* 1421 kg/m^3 at 19.3°C

Method OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Gas comparison pycnometer
Test Facility RCC (2005a)

Vapour Pressure 8.36 x 10^{-14} kPa at 25°C

Method OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Calculated using the modified Watson correlation
Test Facility RCC (2004b)

Surface Tension 67.9 mN/m at 20.7°C

Method OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.
Tensiometer – ring method
Remarks Concentration: 90% of saturation concentration in water
Test Facility RCC (2004e)

Particle Size*

Method EC guidance document (1996) – Particle size distribution, fibre length and diameter distribution
Laser diffraction

Range (μm)	*Mass (%)*
0.5	7.15
1.0	37.99
2.0	78.57
5.0	98.48
10.0	99.82
20.0	99.96
28.0	100.00

Remarks Results represent an average of four separate runs.
Mass median diameter (MMD) = 1.2 μm.
The particle size distribution was found to range from approximately 0.3 μm to 40 μm.
Test Facility RCC (2005e)

Flammability* Not highly flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks The test substance could not be ignited with a flame.
Test Facility RCC (2004c)

Autoignition Temperature* 316°C

Method	EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Test Facility	RCC (2005f)

Explosive Properties Not explosive

Method	UN recommendation criteria
Remarks	Expert statement
Test Facility	RCC (2004d)

Oxidising Properties Not oxidising

Method	UN recommendation criteria
Remarks	Expert statement
Test Facility	RCC (2004f)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – dermal

TEST SUBSTANCE	Mixture containing the notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/ HanBrl: WIST (SPF)
Vehicle	Corn oil
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Marked pink staining of skin was noted in all animals on test day 2. The staining persisted at a slight degree in males up to test days 10, 11, 14 or 15 and in all females up to test day 15 (end of the observation period).
Signs of Toxicity - Systemic	No systemic signs of toxicity were observed during the course of the study. No deaths occurred during the study.
Effects in Organs	No macroscopic findings were recorded at necropsy.
Remarks - Results	None

CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	RCC (2004h)

B.2. Irritation – skin

TEST SUBSTANCE	Mixture containing the 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	1 male, 2 females
Vehicle	None. Moistened with purified water prior to application.
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	Due to the marked staining caused by the test substance, assessment of erythema/eschar was not possible in all animals at the 1 and 24 hour reading, in 2 animals at the 48 hour reading and in one animal at the 72 hour. Therefore, no mean erythema/eschar score of the 3 animals could be calculated. The mean score for oedema was 0 for all three animals. Slight to marked red staining was observed in all animals from 1 hour until 10 days, though slight staining also persisted in two animals until the end of the observation period (14 days).
CONCLUSION	The notified chemical is assumed to be at most slightly irritating to the

skin.

TEST FACILITY RCC (2004i)

B.3. Irritation – eye

TEST SUBSTANCE Mixture containing the 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 1 male, 2 females
Observation Period 72 hours
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	0	0.3	1	< 48 hr	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	0	-	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results Slight reddening of the conjunctivae was observed in two animals one hour after treatment and this persisted until the 24 hour examination in one of the animals. Slight reddening of the sclerae was present in all animals at the one hour reading only. Slight ocular discharge was noted in one animal at the one hour observation only.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY RCC (2004j)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Mixture containing the notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/ CBA/CaOlaHsd
Vehicle Ethanol:water, 7:3 (v/v)
Remarks - Method No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	135	1.0
2.5	114	0.8
5	183	1.4
10	148	1.1
Positive Control (α-hexylcinnamaldehyde)		
0	192	1.0

5	513	2.7
10	655	3.4
25	2382	12.4

Remarks - Results: Slight ear swelling was observed on the second application day at both dosing sites in all mice treated with 5% and 10% test substance. This persisted for 4 days in all animals except for one of the animals in the 10% treatment group in which it remained until the end of the in-life phase of the study (day 5).

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical at up to 10% concentration.

TEST FACILITY: RCC (2004k)

B.5. Repeat dose toxicity

TEST SUBSTANCE: Mixture containing the 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/ HanBrl:WIST (SPF)
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: PEG 300
Remarks - Method: No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 F, 5 M	0	0
low dose	5 F, 5 M	50	0
mid dose	5 F, 5 M	200	0
high dose	5 F, 5 M	1000	0
control recovery	5 F, 5 M	0	0
high dose recovery	5 F, 5 M	1000	0

Mortality and Time to Death
All animals survived until scheduled necropsy.

Clinical Observations
Animals treated with the test item at all dose levels displayed dark red colouration of their faeces. This was observed to reverse during the recovery period.

No other significant treatment related findings were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Males and females of the high dose group displayed statistically significantly higher concentrations of eosinophils and basophils, respectively, following the recovery period. It is noted that the dose response relationship of these effects could not be established as there were no low or mid dose animals observed post recovery. In addition, the study authors note that these parameters were within the historical control values and thus they are unlikely to be toxicologically relevance.

There were some increases observed in some blood chemistry parameters, including calcium, glucose and protein concentrations. These effects were not dose related and the study authors note that the differences were

within the 95% tolerance limit of the historical control data and thus were not considered to be significant.

No changes of toxicological relevance were observed in the urinalysis parameters after the treatment with the test item and the recovery period in both males and females, at any dose level tested.

Effects in Organs

There were some statistically significant changes in organ weights of males after the treatment period, including:

- Decreased thymus- and heart-to-body weight ratios in the low dose group.
- Decreased absolute thymus weight in the high dose group
- Decreased thymus-to-brain weight ratio in high dose group.

Following the recovery period, high dose males displayed increased absolute liver weight, increased liver-to-body weight ratio and liver-to-brain weight ratios. High dose females following recovery, displayed decreased absolute spleen weight and spleen-to-brain weight ratios.

In light of the absence of corresponding microscopical changes and in many cases, a lack of a dose related response, these changes were not considered to be of toxicological relevance.

Tiny pink coloured and birefringent granules were recorded in the lumen of the gastrointestinal tract of most animals of the high dose group (1000 mg/kg/day). Without any tissue reaction these particles were regarded to represent residues of the administered test item. At the end of the recovery period the material was no longer present.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on the absence of any toxicologically significant effects at this dosage level.

TEST FACILITY RCC (2005g)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE Mixture containing the notified chemical

METHOD

	OECD TG 471 Bacterial Reverse Mutation Test.
	Plate incorporation procedure and Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100
	E. coli: WP2uvrA
Metabolic Activation System	Phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in	a) With metabolic activation: 3 to 5000 µg/plate
Main Test	b) Without metabolic activation: 3 to 5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations.

RESULTS

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

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

TEST FACILITY RCC (2004l)

B.7. Genotoxicity – in vitro

TEST SUBSTANCE	Mixture containing the 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	V79 lung cells
Metabolic Activation System	S9 mix prepared from Phenobarbital/β-Naphthoflavone induced rat liver
Vehicle	Suspended in dimethylsulfoxide
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0.94*, 1.88*, 3.75*, 7.50, 15.0, 300.0	4 hr	18 hr
Test 2	0.31, 0.63*, 1.25*, 2.50*, 5.00*, 10.00*	18 hr	18 hr
Test 3	1.25*, 2.50*, 5.00*, 10.00*	28 hr	28 hr
Present			
Test 1	0.94*, 1.88*, 3.75*, 7.50, 15.0, 300.0	4 hr	18 hr
Test 2	0.31, 0.63, 1.25*, 2.50*, 5.00*, 10.00*	4 hr	28 hr

*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	> 36.76	> 300.0	≥ 3.75	Negative
Test 2		> 10.00	≥ 5.00	Negative
Test 3		> 10.00	≥ 5.00	Negative
Present				
Test 1	> 294.10	> 15.00	≥ 1.88	Negative
Test 2		> 10.00	≥ 5.00	Negative

Remarks - Results	No biologically relevant increases in the number of cells with structural chromosomal aberrations were observed as a result of treatment. Note that at several of the concentrations scored for chromosomal aberrations precipitation of the test substance occurred. No relevant increase in the frequency of polyploidy metaphases was observed following treatment compared to controls.
CONCLUSION	The notified chemical was not clastogenic to V79 Chinese Hamster lung cells treated in vitro under the conditions of the test.
TEST FACILITY	RCC (2005h)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Mixture containing the notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – 96-Hour Semi-static Test. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – 96-Hour Semi-static Test.
Species	Zebra Fish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	196 mg $CaCO_3$/L
Analytical Monitoring	None
Remarks – Method	A range finding test was performed. A 100 mg/L test substance concentration was prepared. Due to the low water solubility of the test substance, dispersion remained after 96 h of stirring. The test medium was filtered. No analytical determination of the test substance concentration in the test medium was performed due to the low solubility of the substance in the medium and derivatisation difficulties. The test conditions of exposure were valid.

RESULTS

Concentration mg/L Nominal	*Number of Fish*	*Mortality*				
		3 h	*24 h*	*48 h*	*72 h*	*96 h*
Control	7	0	0	0	0	0
100	7	0	0	0	0	0

LC50	>limit of solubility
NOEC	limit of solubility.
Remarks – Results	After 96 hours of exposure, there was no fish mortality in the control thereby validating the test for this criteria. There was also no fish mortality or other visible abnormalities in the test substance vessel. The test substance had no acute effects on zebra fish up to the solubility limit in test water.
CONCLUSION	The test substance, and by inference, the notified chemical, is not harmful to *Brachydanio rerio* up to its limit of solubility in water.
TEST FACILITY	RCC Ltd (2005i)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Mixture containing the notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – 48-Hour Immobilization Test EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – 48-Hour Immobilization Test
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	None
Remarks - Method	A range finding test was performed. The test medium was prepared according to the method described above in the fish study.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0	0
100	20	0	0

LC50	> limit of solubility
NOEC	limit of solubility
Remarks - Results	The dissolved oxygen concentration is >3 mg/L and there were no immobilised daphnids in the control thereby validating the test. No immobilised daphnids or symptoms of toxicity were observed after 48 hours in the test vessel. The test substance had no acute toxic effects on *Daphnia magna* up to its solubility limit in water under the present conditions of the test.
CONCLUSION	The test substance, and by inference, the notified chemical is not harmful to *Daphnia magna* up to its limit of solubility in water.
TEST FACILITY	RCC Ltd (2004m)

C.2.3. Algal growth inhibition test (Study 1)

TEST SUBSTANCE	Mixture containing notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Desmodesmus subspicatus (Formerly known as Scenedesmus subspicatus)*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0, 3.2, 10, 32 and 100 mg/L Actual: Not determined
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	The concentrations of the test substance in the test solutions were measured at 0 and 72 hours by HPLC and Fluorescence-detection. The measured test substance concentrations even with a loading rate of 100 mg/L were below the limit of quantification (LOQ) of 0.065 mg/L at the start and the end of the test.
Remarks - Method	The algal cell densities were determined by counting with an electronic particle counter (Coulter Counter). The test solutions were prepared by mixing various amounts of test substance in water by ultrasonic treatment for 15 minutes and intense stirring for 96 hours at room temperature in the dark. The filtrates were tested on the algae in three replicates. Each replicate test vessel was inoculated to give an initial cell density of 1.00 x 10^4 cells/mL. The test solutions were clear and colorless.

RESULTS

Biomass		*Growth*	
E_bC50 at 72h	*NOEC*	*E_rC50 at 72 h*	*NOEC*
> limit of solubility	<limit of solubility*	> limit of solubility	<limit of solubility*

*These results are not reliable since an effect was observed in some test vessels but not in others at "higher" concentrations.

Remarks - Results	The microscopic examination of the algal cells after 72 hours showed no

difference in shape and size between algae growing in the highest tested concentration and the control. The 72-hour EC50 for inhibition in biomass and growth rate was above the solubility limit of the notified chemical. The test validity criteria were met.

CONCLUSION The test substance, and by inference, the notified chemical is not harmful to *Scenedesmus subspicatus* at the limit of its solubility in water.

TEST FACILITY RCC Ltd (2005j)

C.2.4. Algal growth inhibition test (Study 2)

TEST SUBSTANCE Mixture containing notified chemical

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

Species	*Desmodesmus subspicatus (Formerly known as Scenedesmus subspicatus)*
Exposure Period	72 hours
Concentration Range	100 mg/L
Actual	Not determined
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	Cell densities were determined by a UV/VIS spectrophotometer.
Remarks - Method	A range finding test was performed. The test medium was prepared as described above in the fish study. Each replicate test vessel (3 replicates) was inoculated to give an initial cell density of 0.5-0.85 µg dry weight/mL which is equivalent to OD680 of about 0.010. Cell concentrations were determined at 0, 24, 48 and 72 hours. Test conditions were: 22 ± 2°C, continuous illumination, and pH 8 ± 0.2. A Student's t-test was used for statistical analysis.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
> limit of solubility	limit of solubility	> limit of solubility	limit of solubility

Remarks - Results There was no growth inhibition with respect to algal yield (biomass) and algal growth rate as compared to the control. The 72-hour EC50 for inhibition in biomass and growth rate was greater than the solubility limit. The test validity criteria were met.

CONCLUSION The test substance, and by inference, the notified chemical is not harmful to *Desmodesmus subspicatus* up to its limit of solubility.

TEST FACILITY BMG Engineering Ltd (2008)

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