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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

IRGACURE 127

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Director
NICNAS

TABLE OF CONTENTS

FULL PUBLIC REPORT

IRGACURE 127

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Ciba Specialty Chemicals (ABN: 97 005 061 469)
235 Settlement Road
THOMASTOWN VIC 3082

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 Formula
Structural Formula
Molecular Weight
Spectral Data
Non-hazardous Impurities (>1%)
Percentage of notified chemical in end-use preparations
Import Volumes
Identity of sites of reformulation

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
France (03-01-0792-01)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
IRGACURE 127

METHODS OF DETECTION AND DETERMINATION

METHOD	^{1}H-Nuclear Magnetic Resonance spectroscopy Electrospray Ionisation Mass Spectrum Infrared Spectroscopy Elemental Composition
Remarks	Reference spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
>90%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	isomer of notified chemical		
CAS No.	-	*Weight %*	1.1%
Hazardous Properties	May have chronic toxicity, based on structural similarity to notified chemical.		

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in 20 kg lined paper bags in cardboard boxes.

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

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

USE
The notified chemical is used as a component of overprint varnishes for paper in the publication industry.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne.

TRANSPORTATION AND PACKAGING
Boxes containing the notified chemical will be transported by road from wharf to the notifier's site and stored. No repackaging operations will be carried out at the notifier's site. The notified chemical will then be transported by road unopened to the varnish formulation sites.

5.2. Operation description

Varnish manufacture
At the varnish formulation sites the 20 kg bags containing the notified chemical are removed from boxes and manually transferred to a weighing station under a dust extractor. The contents are weighed and then manually poured, with other ingredients, into a mill and mixed to produce the overprint varnish. Laboratory technicians at the varnish manufacturing site will be involved in quality control checks on the overprint varnish. The finished products containing <1% of the notified chemical, are then pumped to filling machines for filling into 20 kg metal pails. This process is carried out in bunded and enclosed areas with local exhaust ventilation. The closed containers are manually put on pallets and taken by forklift to the warehouse for storage and distribution. The varnish is distributed to the printing industry for coating paper (i.e. magazine covers to give them clear glossy look). The formulation machinery is cleaned out periodically with suitable solvents.

Application of varnish
Overprint varnish containing the notified chemical will be used in Publication Gravure, Offset and Lithographic printing processes. The varnish is fed to the print machine directly from the 20 kg metal pails through controlled pressure. The varnish is then applied onto paper via an automatic coating machine and sealed under an impermeable top coat to produce the final product, such as glossy magazine covers. Excess varnish is returned to the metal pails.

Cleaning of printing machine
Cleaning of the print machine involves removal of excess varnish to containers for re-use, running the

paper substrate back and forth and finally wiping machine with suitable solvent. The solvent wet rags are collected in a metal fire-resistant closed container for disposal.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and storage			
Transport and warehouse workers	2	4 hours/day	200 days/year
Reformulation			
Blending operators	20	8 hours/day	25 days/year
Filling of varnish	20	8 hours/day	25 days/year
Quality control staffs	8-15	6-8 hours/day	20 days/year
Cleaning of equipment	20	8 hour/day	2 days/year
Varnish Application			
Addition of varnish to print machine	50	4 hours/day	300 days/year
Cleaning of equipment	10	8 hour/day	10 days/year

Exposure Details

Transport and storage

Transports and warehouse workers will be exposed to the notified chemical only in the event of a spill or if packaging is accidentally breached.

Varnish Manufacture

Dermal, ocular and inhalation exposure to the notified chemical is possible when manually loading the powder into the mixing vessel. The loading operation is carried out under a dust extractor and blending occurs in a closed mixing tank under local exhaust ventilation. During these steps, workers will wear personal protective equipment including coveralls, gloves and eye protection. These operations are also carried out under specially lit conditions in order to reduce photodegradation of the product.

Intermittent dermal exposure to the varnish preparations is possible when collecting samples for quality testing. Laboratory workers will wear laboratory coats, gloves and eye protection.

Workers may also be exposed to drips and spills when drumming off the varnish and while connecting and disconnecting filling pipes and during cleaning. Workers will wear coveralls, gloves and eye protection when carrying out these activities.

Varnish Application

During the printing process dermal and ocular contact may occur when opening and handling the varnish containers, when introducing the varnish into the print machine, during intermittent contact with printing rollers and from cleaning operations and contact with contaminated rags. Inhalation exposure is also possible if aerosols are formed. Exposure to the notified chemical will be limited due to personal protective equipment (coveralls, goggles, impervious gloves and safety boots) worn by workers.

After application to paper substrate and once dried, the varnish containing the notified chemical is cured into an inert matrix and hence is not bioavailable.

Cleaning of equipment

Cleaning of the print machine involves removal of excess varnish to containers for re-use, running the paper substrate back and forth and finally wiping machine with suitable solvent. Workers involved in cleaning of equipment will wear gloves and coveralls.

5.4. Release

RELEASE OF CHEMICAL AT SITE

Release to the environment may occur at the notifier's site in the unlikely event of an accident during transport or if the packaging is damaged.

The notified chemical will be used in the formulation of overprint varnish used for paper coating (e.g. magazine covers to give them a glossy look). During this process release could occur during transport and spills and represents a loss of less than 1% (maximum of 50 kg of notified chemical annually). In the case of a spill it is likely that the material will be recycled back into the process if not contaminated. If contaminated then the material will be collected into a suitable labelled container for storage and disposal to landfill by a licensed contractor. The site of the spill is washed and any cleaning effluent is absorbed and disposed of with the spilt material.

During formulation of overprint varnish, <250 kg/annum of the notified chemical waste will be generated from cleaning of equipment. The residues in the imported paper bags are expected to contain up to 0.5% of the notified chemical (maximum of 25 kg of notified chemical annually). The imported bags are incinerated by licensed waste disposal contractors.

RELEASE OF CHEMICAL FROM USE

Good work practises are expected to minimise spillage during the printing process, but solvent waste containing the notified chemical will be generated in cleaning ink application (including wet rags used to clean equipment). It is expected that less than 250 kg (5%) of the notified chemical will be collected by licensed waste disposal contractors for incineration.

Very little of the notified chemical will be released to water under normal operation conditions. Considering the worst case, 1% of the notified chemical will reach the aquatic compartment due to the coating process.

5.5. Disposal

Most of the waste chemical resulting from the ink manufacture and printing processes, including the import paper bag residues, is expected to be disposed of by incineration. Residual chemical left in metal pails will be disposed of to landfill. Solvent containing ink wastes is recycled.

The majority of the imported chemical will be bound to paper, which will be disposed of to landfill, recycled or incinerated.

5.6. Public exposure

Members of the public may be exposed to the notified chemical through handling of paper which has been printed with the varnish (<1% notified chemical). The notified chemical will be encapsulated in the varnish, and an impermeable top coat will be applied over the varnish, and thus the notified chemical will not be bioavailable.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa	Slightly yellow powder
Melting Point	84.3ºC ± 0.5ºC
METHOD	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Melting point was determined using the capillary method.
TEST FACILITY	RCC Ltd (2003a)

Boiling Point 332.7ºC ± 0.3ºC at 97.3 kPa

METHOD OECD TG 103 Boiling Point.
EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Boiling point was determined using the capillary method.
TEST FACILITY RCC Ltd (2003b)

Density 1195 kg/m^3 at 19.7ºC ± 0.3ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks Density was determined using a gas comparison pyknometer.
TEST FACILITY RCC Ltd (2003c)

Vapour Pressure << 1.6 x 10^{-7} kPa at 25ºC

METHOD OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was determined by applying the gas saturation method. The experiment was performed at 50, 60 and 70°C based on the results of the vapour pressure model calculated using the Modified Watson Correlation. No evaporated notified chemical could be detected at up to 70ºC.

The notified chemical is considered to be slightly volatile (Mensink *et al*., 1995).
TEST FACILITY RCC Ltd (2003d)

Water Solubility 9.9 mg/L at 20ºC (standard deviation ± 1.1 mg/L)

METHOD OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The saturation concentration of the notified chemical at room temperature was estimated by a simplified flask method in the preliminary test to be higher than 10^{-2} g/L. Therefore, the flask shaking test was performed using 5 g notified chemical in 25 mL water and a shaking time of 24, 48 and 72 h at 30°C. Flasks were equilibrated for 24 h at 20ºC prior to analysis by HPLC with UV Detection.

The notified chemical is considered to be slightly soluble (Mensink et al 1995).
TEST FACILITY RCC Ltd (2003e)

Hydrolysis as a Function of pH The notified chemical is hydrolytically stable

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

pH	*Initial Concentration Measured (µg/ml)*	*Concentration measured after 2.4 hours incubation (µg/ml)*	*Concentration measured after 5 days incubation (µg/ml)*
4	20.47	19.38	20.99
	19.67	17.92	21.38
7	10.79	11.18	10.29
	10.68	10.27	11.80
9	20.36	20.87	19.51
	19.36	20.59	19.73

Based on the measured concentrations it can be stated that the test item is stable under the conditions of the test.

Remarks Hydrolysis testing at pH 4.0, pH 7.0 and pH 9.0 indicated that there was no significant degradation of the notified chemical at 50ºC with concentrations within 10% of the initial value after 5 days. Based on the measured concentrations (see table above) it can be stated that the test item is hydrolytically stable under the conditions of the test and no further testing was conducted.

TEST FACILITY RCC Ltd (2003f)

Fat (or n-octanol) Solubility 11.27 g/kg ± 0.5 g/kg HB 307 at 37°C

METHOD Directive 84/449/EEC, A.7 Fat Solubility (1984) and the OECD TG 116 Fat Solubility of Solid and Liquid Substances (1981) using a simplified flask method.

Remarks In a preliminary test the miscibility of the test item and the fat was tested. Since the test item was not miscible with the standard fat in a 1:1 ratio the main test was performed.

In the main test the solubility of the test item in standard fat at 37°C with preliminary equilibration at 30°C or 50°C for 24 hours was tested.

TEST FACILITY RCC Ltd (2003g)

Partition Coefficient (n-octanol/water) log Pow at 25ºC = 2.3

METHOD OECD TG 117 Partition Coefficient (n-octanol/water), HPLC Method.
EC Directive 92/69/EEC A.8 Partition Coefficient.

Remarks In the preliminary test the $\log P_{o/w}$ was estimated to be 4 based on ratio of solubility in octanol and water. The HPLC method was used to conduct the main test.

Based on the $\log P_{o/w}$ of 2.3, the notified chemical is likely to partition to the octanol phase.

TEST FACILITY RCC Ltd (2003h)

Adsorption/Desorption – screening test $\log K_{oc}$ = 2.02 at 25°C.

METHOD OECD Guideline for the Testing of Chemicals, No. 121, Estimation of the Adsorption Coefficient (Koc) on Soil and Sewage Sludge using High Performance Liquid Chromatography (HPLC), Adopted Test Guideline (January 2001)
EC Directive 2001/59 C.19 Absorption Co-efficient of Annex V

Remarks The adsorption coefficient was estimated to be 104 using the HPLC method. This value indicates that the notified chemical is moderately mobile.

TEST FACILITY RCC Ltd (2003i)

Dissociation Constant pK_a= 12.8

Remarks The dissociation constant was estimated from the molecular structure.

TEST FACILITY RCC Ltd (2003j)

Surface Tension 67.3 mN/m at 20.3ºC ± 0.1 ºC

METHOD OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.

Remarks Surface tension was determined for a 90% saturated solution of the notified chemical, using a ring tensiometer. The notified chemical is not a surface active substance, as the surface tension is over 60 mN/m.

TEST FACILITY RCC Ltd (2003k)

Particle Size Mass median diameter: 16.8 µm

METHOD EC Guidance document ECB/TM/February 1996.

Range (µm)	*Mass (%)*
<2	5.31
2-6	6.13
6-10	7.14
10-14	15.66
14-18	22.41
18-22	20.39
22-24	7.33
24-28	9.89
28-40	5.74
>40	0

Remarks Respirable fraction (<10 µm): 18.58%
Inspirable fraction (<100 µm): 100%

Particle size was determined using the laser scanning/diffraction method, on a sample of test substance suspended in white spirit containing Sympatens SHO/400. Microscopic examination showed that the powder consists of elongate, squared, colourless, crystalline structures.

TEST FACILITY RCC Ltd (2003l)

Flash Point Not determined.

Remarks Test not conducted on a solid.

Flammability Limits Not highly flammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).

Remarks The notified chemical could not be ignited with a gas flame after 2 minutes contact time, but instead melted, evolving sparks. A yellow melt remained. Therefore, no main test was performed.

TEST FACILITY RCC Ltd (2003m)

Autoignition Temperature >400°C

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.

Remarks There was no relevant exothermic reaction observed below 400°C, the limit of the test. At the end of the measurement the notified chemical was a black liquid.

TEST FACILITY RCC Ltd (2003n)

Explosive Properties Not explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.

Remarks A negative result is predicted on structural grounds. The oxygen balance was calculated as about –235, which is below the limit of –200 requiring experimental testing.

TEST FACILITY RCC Ltd (2003o)

Reactivity

Remarks Notified chemical is light-sensitive.

Oxidising Properties Non-oxidising.

METHOD	Screened based on the UN Recommendations on the transport of Dangerous Goods.
Remarks	The notified chemical contains oxygen, which is chemically bound only to carbon or hydrogen, and thus is found to be non-oxidising.
TEST FACILITY	RCC Ltd (2003p)

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 >2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 >2000 mg/kg bw	low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Local lymph node assay skin sensitisation	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 5 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration	genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus	non genotoxic

7.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
EC Directive 96/54/EEC B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.

Species/Strain	Rat/HanBrl: Wist (SPF)
Vehicle	Polyethylene glycol 3000 (PEG 300)
Remarks – Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3/sex	2000	0

LD50	> 2000 mg/kg bw
Signs of Toxicity	Hunched posture and ruffled fur was observed in all animals for the first 5 hours following exposure, and from days 8 to 15. Also, the majority of animals exhibited these symptoms between the 5-hour observation and day 8. Body weight loss was seen in all animals. For males, a moderate body weight loss (19 to 26%) was observed over the study. The females all showed weight loss in week 1 (7 to 15%). At day 15, one female showed a 7% weight increase, and the other two showed decreases (3% and 25%) as compared to the starting weights.
Effects in Organs	No macroscopic findings were recorded at necropsy.
Remarks – Results	None.

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

TEST FACILITY: RCC Ltd (2003q)

7.2. Acute toxicity – dermal

TEST SUBSTANCE: 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	Polyethylene glycol 300 (PEG 300)
Type of dressing	Semi-occlusive.
Remarks – Method	The application period was 24 hours.

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of toxicity were observed during the study period.
Effects in Organs	No macroscopic findings were observed at necropsy.
Remarks – Results	None.

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

TEST FACILITY RCC Ltd. (2003r)

7.3. Acute toxicity – inhalation

Not performed.

7.4. Irritation – skin

TEST SUBSTANCE Notified chemical.

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White SPF
Number of Animals	3/sex
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks – Method	Notified chemical was moistened with water and applied to the intact left flank of each rabbit.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	0	0	-	0
Oedema	0	0	-	0

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

Remarks – Results None.

CONCLUSION The notified chemical is non-irritating to skin.

TEST FACILITY RCC Ltd. (2003s)

7.5. Irritation – eye

TEST SUBSTANCE Notified chemical.

METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 hours
Remarks – Method	0.1 g was instilled into the left eye of each rabbit.

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	1.3	0.3	1	2	48 hours	0
Conjunctiva: chemosis	0	0	0	2	1 hour	0
Corneal opacity	0	0	0	1	1 hour	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: Corneal opacity, covering the whole eye, was observed in one animal at the 1-hour observation. Assessment of the sclerae was not possible in one animal at the 1-hour examination due to marked swelling of the conjunctivae. Mucus was present in the treated eye of one animal at the 24-hour examination.

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

TEST FACILITY: RCC Ltd. (2003t)

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

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain: Mouse / CBA/CaOlaHsd
Vehicle: Acetone:olive oil, 4:1
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)	544	1
1	649	1.2
2.5	653	1.2
5	658	1.2
Positive Control		
0	529	1
5	1521	2.9
10	1372	2.6
25	3732	7.1

Remarks - Results: On the second application day, slight to moderate swelling and slight to moderate erythema were observed at both dosing sites in all mice being treated with 2.5 and 5% (w/w) notified chemical, persisting for 4-5 days. The positive control chemical was α-hexylcinnamaldehyde in acetone:olive oil, 4:1.

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

TEST FACILITY: RCC Ltd. (2003u)

7.7. Repeat dose toxicity - oral

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/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	An additional high dose group, treated with 100 mg/kg bw/day was introduced because the evaluation of the initial high dose group (160 mg/kg bw/day) was not possible due to deaths of animals. Animals in the initial high dose recovery group were sacrificed at the end of the main test, and animals in the 100 mg/kg bw/day group were used for the 2-week recovery period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10 / sex	0	0
II (low dose)	5 / sex	5	0
III (mid dose)	5 / sex	50	0
IV (high dose)	10 / sex	160	7/10 males, 6/10 females
V (alternative high dose)	10 / sex	100	1/10 males, 2/10 females
VI (control recovery)	5 / sex	0	0
VIII (alternative high dose recovery)	5 / sex	100	0

Mortality and Time to Death

7 animals treated with 160 mg/kg bw/day died spontaneously (days 6_f, 12_m, 14_m, 18_m, 20_f, 24_f, 25_m)
6 animals treated with 160 mg/kg bw/day were killed for ethical reasons (days 14_f, 15_f, 17_f, 18_m, 25_m, 25_m)

2 animals treated with 100 mg/kg bw/day died spontaneously (days 10_m, 19_f)
1 animal treated with 100 mg/kg bw/day was killed for ethical reasons (day 13_f)

Clinical Observations

There were a number of observations that were regraded as unrelated to treatment with the notified chemical, and these have not been mentioned here.

160 mg/kg bw/day

- During treatment, moderate piloerection was seen on at least one occasion in 8 females, and slight piloerection in 4 males and 7 females.
- Severe sedation was seen in 1 male on day 7. Slight to moderate sedation was seen in 3 males and 3 females, lasting for >8 days in these animals.
- Slight to moderate emaciation was noted in up to 5 males and up to 6 females beginning early in the 2nd week and continuing until the end of treatment.
- Slightly to moderately hardened abdomen was noted in 2 males and in 5 females during weeks 3 and 4 of treatment.
- Significantly decreased mean locomotor activity (tested in week 4) was noted in both males and females when compared with controls.
- The mean absolute food consumption was reduced to about 60%, the mean relative food consumption to about 70% of the control values in males during the whole test period and in females over weeks 1-3.
- The mean absolute body weights and the body weight gains were decreased in males when compared with controls during treatment weeks 2 to 4. In females the mean absolute body weights were decreased in treatment weeks 3 and 4, and mean body weight gains were decreased in weeks 2, 3 and 4.
- A statistically significant response was not seen in the grip strength results. However, there was a

noticeable decrease compared with controls, and the statistical significance for the 100 mg/kg bw/day group suggests that this observation was test-substance related.

100 mg/kg bw/day
- Slight to moderate piloerection was seen in two males and one female during treatment, and in one male on the first day of the recovery period.
- Severe sedation was seen in 1 female on day 19. Slight sedation was seen in 1 male (2 days) and 1 female (1 day).
- Slight emaciation was noted in 1 female throughout week 2.
- Slightly hardened abdomen was noted for 1 male during weeks 3 and 4, and for the first week of the recovery period.
- Significantly decreased ($p<0.01$) mean fore and hind limb grip strength was noted in females, and mean fore limb grip strength in males ($p<0.05$), when compared with controls.
- Significantly decreased mean locomotor activity (tested in week 4) was noted in males when compared with controls. Significantly increased mean locomotor activity was noted in females, however this was considered to be due to relatively low control values.

50 mg/kg bw/day
- Any observed changes were not attributed to the notified chemical.

5 mg/kg bw/day
- One male (No. 15) exhibited slight to moderate piloerection and pale skin for weeks 3 and 4, hunched posture and slight to moderate emaciation during week 4, and reduced fore and hind limb grip strength.
- Any observed changes to other animals in the group were not attributed to the notified chemical.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology

160 mg/kg bw/day
- The low number of surviving animals makes statistical evaluation difficult.
- Decreased corpuscular hemoglobin was observed in females at week 4.
- Mean reticulocyte maturity index (medium fluorescence) was decreased in males at week 4.

100 mg/kg bw/day
- Decreased mean corpuscular volume was noted in males and females at week 4, and there was a compensating increase in mean corpuscular hemoglobin concentration for these animals. This increase in mean corpuscular hemoglobin persisted in males for the two-week recovery period.
- The mean relative and absolute level of monocytes was increased in males at week 4.
- Mean reticulocyte maturity index (medium fluorescence) was decreased in males and females at week 4. Mean reticulocyte maturity index (high fluorescence) was increased in males and females at week 4.
- The mean level of methaemoglobin was decreased in males and females at week 4. This decreased level persisted in both sexes after the two-week recovery period.
- The prothrombin time was increased in males at week 4 and after the two-week recovery period. The activated partial thromboplastin time was decreased in males and females at week 4.

50 mg/kg bw/day
- Any observed changes were not attributed to the notified chemical.

5 mg/kg bw/day
- The total leukocyte count and mean absolute level of lymphocytes were markedly decreased in animal No. 15.
- Any observed changes to other animals in the group were not attributed to the notified chemical.

Clinical Biochemistry

160 mg/kg bw/day
- The mean activity of glutamate dehydrogenase was significantly increased in females at week 4.
- The mean level of cholesterol, triglycerides and phospholipids were significantly increased in females at week 4.
- Mean urea was increased by 12.5% in males, however this change was not statistically significant and no increase was seen in females.

- Mean calcium was increased by 8% in females, a change that was statistically significant. Calcium was also increased 3% in males, however this was not statistically significant.
- Mean potassium, sodium and chloride levels were not noticeably affected.

100 mg/kg bw/day
- The mean activities of lactate dehydrogenase and glutamate dehydrogenase were significantly increased in males after 4 weeks
- A statistically significant rise of 19% in mean urea was seen in males, and a non-significant rise of 13% in females.
- Mean calcium was increased 3% in males, however this was not statistically significant.
- Mean potassium was up 8% in males at the end of both the main study and the recovery period, with the increase attaining statistical significance in the recovery period. Mean sodium increased 4% in males and 1.5% in females, both of which were statistically significant. Mean chloride was increased in females by 1.5% at the end of the study period (not statistically significant), and in females by 5% and males by 9% after the recovery period, both of which were statistically significant.

50 mg/kg bw/day
- The activity of lactate dehydrogenase was significantly decreased in females
- Mean urea was increased by 10% in males and 12% in females, although these increases were not statistically significant.
- A statistically significant increase in mean calcium of 4.5% was seen in males.
- Mean potassium, sodium and chloride levels were not noticeably affected.

5 mg/kg bw/day
- Any observed changes were not attributed to the notified chemical.

Urinalysis
160 mg/kg bw/day
- The mean relative density of the urine was increased by 1.5% in females, however this was not statistically significant.
- Urinary protein was increased by 19.5% in males and decreased by 25% in females.

100 mg/kg bw/day
- The mean relative density of the urine was significantly increased by 3.5% in males, and a minor increase of 0.5% was noted in females.
- Urinary protein was decreased by 10% in males and increased by 25% in females.

50 mg/kg bw/day
- The mean relative density of the urine was significantly increased by 4% in females, and increased (not significantly) by 1.5% in males.
- Urinary protein was increased by 15.5% in males and by 120% in females (statistically significant).

5 mg/kg bw/day
- Urinary protein was increased by 40% in females.

Effects in Organs
Macroscopic Findings
160 mg/kg bw/day
- The number of surviving animals in the 160 mg/kg bw/day group at day 28 was too low for many statistical evaluations.
- At week 4, there were significant changes in absolute and/or relative organ weights for the liver (increase) and thymus (decrease) in males and females, and in the kidney (increase) in females only.
- At necroscopy, both sexes showed emaciation (7m, 5f), reduced thymus size (9m, 7f), black brown stomach contents (2m. 2f) and reduced mandibular lymph node size (3m, 1f). In addition, males showed reduced prostate (4m) and pancreas size (1m), and females showed reduced size of the uterus horns (1f) and red discoloration of gastric fundus (2f).
- The above observations were mainly restricted to animals that died before the end of the study. Of the 3 males that survived to Day 28, two showed only reduced thymus size, and one showed no macroscopic organ differences. Of the females that survived to Day 28, 2/4 had no abnormal findings, 1/4 exhibited only reduced thymus size, and 1/4 exhibited reduced thymus size and red discoloration of gastric fundus.

100 mg/kg bw/day

- At week 4, there was a significant increase in relative liver weight in both sexes as compared with controls, and an increase in the mean kidney to body weight ratio in females.
- After the two-week recovery period, there were significant increases in absolute and/or relative organ weights for the liver, thymus, adrenal, spleen and kidney in females as compared with controls, and significant changes in absolute and/or relative organ weights for the adrenal (increase) and epididymides (decrease) in males.
- At necroscopy, one male rat that died spontaneously on Day 10 showed a distended stomach and foci associated with the thymus. One female rat that survived until Day 28 showed a discoloured thymus. Females exhibited discoloured thymus and lung and enlargement of the left kidney.
- There were no abnormal macroscopic findings upon necroscopy for the control group.

50 mg/kg bw/day

- At necroscopy, one female exhibited reddish discoloration of the mesenteric lymph node.

5 mg/kg bw/day

- The mean kidney to body weight ratios were increased in females at week 4, however this is considered incidental as there was no significant effect on 5 mg/kg bw/day males or 50 mg/kg bw/day animals of either sex.
- At necroscopy, there were a number of macroscopic findings in Animal No. 15, consisting of: reduced size of liver, testes, epididymides, prostate, seminal vesicles and thymus and an enlarged spleen. In addition, the pancreas and mesenteric lymph node were both gelatinous, and both the mesenteric and mandibular lymph nodes had reddish discolouration. The animal was emaciated and pale, and the abdominal cavity contained watery clear fluid.

Microscopic Findings

Organ	*Effect*[1]	*Control n=20*	*5 mg/kg bw/day n=10*	*50 mg/kg bw/day n=10*	*100 mg/kg bw/day n=10*	*160 mg/kg bw/day n=20*	*100 mg/kg bw/day recovery n=10*
Stomach	Epithelial hyperplasia Hyperkeratosis Erosions/fibrosis of glandular stomach	1m/2f 2f 1m	1m/3f 1m/2f 1m*	5m/1f 5m/3f 1m	1m 1f	2m 6f 8m/6f	1f 1m
Liver	Hepatocellular hypertrophy Fatty change	1m 2f	4m/1f 5m*/5f	4m/4f 3m/3f	1m/3f 1m	5m/7f 1m/1f	3m/2f 4m/4f
Kidneys	Tubular dilation Tubular cell swelling Tubular cell necroses Granular material[2]			2m/1f	1m1/f 1m/3f 1f 1m	3m/1f 1m/3m 1m 1m	3m/3f 1m
Testes	Vacuolation of tubular epithelium Tubular degeneration	1m	1m* 1m*		2m	6m 4m	2m 1m
Prostate	Atrophy		1m*		1m	8m	
Seminal vesicles	Atrophy		1m*		1m	7m	
Uterus	Stromal atrophy				1f	5f	
Vagina	Mucosal atrophy				1f	4f	
Bone marrow	Decreased erythropoiesis[3]					2m/3f	1f
Spleen	Atrophy[4] Atrophy[5]		1m* 1m*	2f	1m/1f 1m/1f	7m/6f 8m/7f	1m 1m
Thymus	Lymphoid atrophy[6]		1m*/1f		1f	9m/6f	
Mesenteric lymph nodes	Lymphoid atrophy[7]		1m*	2f	1m/2f	6m/8f	
Mandibular lymph nodes	Lymphoid atrophy	1f			4f	6m/1f	
Adrenal cortex	Vacuolation of zona fasciculata	1f	3m	4m	4m/1f	8m/4f	1m

	Hypertrophy of zona fasciculata		4f	3m/5f	2m/2f	6m/6f	3m/3f

Findings within the range of background findings typically noted for this strain and age and were not noted here.
*Includes Animal No. 15.
[1]Effects are slight to moderate unless otherwise stated.
[2]Fine tubular granular material, probably representing desquamated epithelial debris.
[3]Slight to markedly decreased erythropoiesis.
[4]Minimal to marked atrophy of the periarteriolar lymphatic sheet.
[5]Minimal to marked atrophy of the marginal zone.
[6]Minimal to severe lymphoid atrophy.
[7]Mesenteric lymphoid atrophy was usually associated with starry sky.

Remarks – Results
Animal No. 15 in the 5 mg/kg bw/day group: This individual rat is most likely an outlier, and thus of no toxicological significance. This conclusion can be drawn by comparison with the other rats in the 5 and 50 mg/kg bw/day groups that did not show any symptoms of toxicity. Also, the poor condition of this rat was unlikely to be caused by the notified chemical as the effects did not match the high-dose rats. Specifically, there was no sign of nephrotoxicity in this rat, however animals receiving higher doses exhibited a strongly dose-dependent nephrotoxic effect.

Treatment with 160 mg/kg bw/day notified chemical was lethal in 65% of animals, and treatment with 100 mg/kg bw/day was lethal in 15% of animals. In two animals, acute tubular cell necrosis in the kidney was identified as a possible cause of death. Further causes of death could be considered as general stressful condition and exhaustion (indicated by findings such as lymphatic atrophy, adrenal hypertrophy).

The NOAEL for the chemical was determined as 5 mg/kg bw/day, based on an adverse nephrotoxic effect. Tubular cell swelling was recorded following necroscopy in animals treated with 50 mg/kg bw/day notified chemical and above. The effect persisted through the recovery period. Clinical biochemistry findings support a nephrotoxic effect in animals treated with 50 mg/kg bw/day but not 5 mg/kg bw/day. Findings in the 50 mg/kg bw/day group included statistically significant changes to lactate dehydrogenase activity, mean calcium, and mean protein content of urine, and relatively large but not statistically significant changes in mean urea and urine density. While many of these findings did not show a strong dose-response relationship, the weight of evidence supports nephrotoxic effects in animals treated with 50 mg/kg bw/day of notified chemical and above. It should be noted that the small number of surviving animals in the 160 mg/kg bw/day group reduces the informative value of statistical significance in this groupand in some cases obfuscates the dose-response relationship.

Significant changes were observed in the liver at all treatment dosages. In the absence of further findings, the hepatocellular hypertrophy and associated microvesicular fatty change are considered to be adaptive metabolic changes. Thus no NOEL can be determined from this test.

Treatment-related changes to the upper digestive tract consisted mainly of gastric erosions in the 160 mg/kg bw/day group. This was considered to be a local portal-of-entry effect.

The general poor health of animals in the 50, 100 and 160 mg/kg bw/day groups was illustrated by the other findings. Animals in the 100 and 160 mg/kg bw/day groups exhibited clinical signs such as piloerection, emaciation, sedation, hunched posture, decreased locomotor activity, decreased food consumption and bodyweight. Mesenteric lymphoid atrophy and splenic atrophy were seen in animals receiving 50 mg/kg bw/day or higher. In the 100 and 160 mg/kg bw/day groups general poor health was further supported by the adaptive response of focal to diffuse minimal to slight cortical hypertrophy of the adrenal gland and lymphoid atrophy in the thymus and mandibular lymph nodes. After the two-week recovery this atrophy was not present, however thymus size was increased in females, both in absolute terms and relative to body and brain weights. Atrophy of the splenic T/B cell areas was observed in animals receiving 50 mg/kg bw/day or more, and was mainly reversed in recovery animals. Decreased erythropoiesis in bone marrow was observed, mainly in the 160 mg/kg bw/day group.

Effects on the reproductive systems were mainly observed in the two high dose groups, and were presumably also related to the general poor health of the animals. These effects were mostly reversed in the recovery group.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 5 mg/kg bw/day in this study, based on an adverse nephrotoxic affect and other general signs of poor health seen in groups treated with 50 mg/kg bw/day and above.
TEST FACILITY RCC Ltd. (2003v)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical.

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

Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA100. *E. coli*: WP2 uvrA.
Metabolic Activation System	Phenobarbital/β-Naphthoflavone induced rat liver S9.
Concentration Range in Main Test	a) With metabolic activation: 33 - 5000 µg/plate. b) Without metabolic activation: 33 - 5000 µg/plate.
Vehicle	DMSO
Remarks – Method	Both a plate incorporation test (Test 1) and pre-incubation test (Test 2) were performed.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Present			
Test 1	None	None reported	None
Test 2	>5000 µg (TA 100)	None reported	None
Absent			
Test 1	>2500 µg (TA 1537)	None reported	None
Test 2	None	None reported	None

Remarks – Results Negative controls were similar to historical values. Positive controls confirmed the sensitivity of the test system.

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

TEST FACILITY RCC Ltd (2002)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.
EC Directive 2000/32/EC B.17 Mutagenicity - *In vitro* Mammalian Cell Chromosome Aberration Test.

Species/Strain	Chinese Hamster
Cell Type/Cell Line	V79 cells
Metabolic Activation System	Phenobarbital/β-Naphthoflavone induced rat liver S9
Vehicle	DMSO
Remarks – Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent	20, 40*, 80*, 120*, 160, 200 µg/mL	4 hours	18 hours

Present	20, 40*, 80*, 120*, 160, 200 µg/mL	4 hours	18 hours

*Cultures selected for metaphase analysis.

Remarks – Results

The chromosomal aberration rates (16% without S9, 22.5% with S9) were increased after treatment with 120 µg/mL as compared to solvent controls (statistically significant and biologically relevant). The number of cells carrying exchanges (8% and 12.5%, respectively) was also distinctly increased as compared to control levels. Furthermore, in the presence of metabolic activation, there was as dose-related increase in the number of aberrant cells. No increase in the frequencies of polyploid metaphases was found after treatment with the test item compared to controls.

Test concentrations up to 200 µg/mL were chosen as precipitation was observed following treatment with 425 µg/mL in the pre-experiment.

Toxic effects indicated by reduced cell numbers and/or mitotic indices of below 50% of control were observed in all tests at all concentrations. At 120 µg/mL, the number of cells was reduced to 11% (without S9) and 26% (with S9) of control values.

Appropriate mutagens were used as positive controls. They induced statistically significant increases in cells with structural chromosome aberrations.

CONCLUSION

The notified chemical was clastogenic to Chinese Hamster V79 cells treated in vitro under the conditions of the test

TEST FACILITY

RCC Ltd. (2003w)

7.10. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse / NMRI
Route of Administration: Single administration/Oral
Vehicle: Corn oil.
Remarks – Method: No significant protocol deviations.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time Hours*
1 (negative control)	5/sex		24
2	5/sex	500	24
3	5/sex	1000	24
4	5/sex	2000	24
5	5/sex	2000	48
6 (positive control)	5/sex	40 (CP)	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity

The majority of animals treated with 2000 mg/kg bw exhibited a reduction in spontaneous activity and/or eyelids closed and/or ruffled fur for up to 48 hours. The majority of animals treated with 1000 mg/kg bw exhibited toxic symptoms for up to 6 hours. Some animals treated with 500 mg/kg bw also exhibited these symptoms for up to 6 hours.

Genotoxic Effects

After treatment with the test item, the number of polychromatic

	erythrocytes was not substantially decreased as compared to the vehicle control. Also, there was no enhancement in the frequency of the detected micronuclei compared to control values.
Remarks – Results	The positive control caused a substantial increase in induced micronucleus frequency.
CONCLUSION	The notified chemical was not clastogenic in this in vivo micronucleus test in the bone marrow cells of mouse under the conditions of the test.
TEST FACILITY	RCC Ltd. (2003x)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD
- Inoculum: Aerobic activated sludge from a wastewater treatment plant (ARA Ergolz II, Füllinsdorf, Switzerland) treating predominantly domestic wastewater.
- Exposure Period: 28-day
- Auxiliary Solvent: None.
- Analytical Monitoring: None.
- Remarks – Method: The % biodegradation of the notified chemical was calculated based on a total carbon content (TOC) of 15 mg C/L test item. For the abiotic control and the abiotic control blank the untreated test medium was poisoned with mercury dichloride at a concentration of 10 mg/L.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*Mean % degradation*	*Day*	*Mean % degradation*
2	-1.3	2	49.0
5	-2.2	5	66.9
7	-2.2	7	72.2
9	-2.5	9	75.0
12	-3.1	12	80.7
14	-2.7	14	84.4
19	-1.5	19	94.5
23	-1.4	23	92.9
27	-2.5	27	94.7
28	-2.3	28	94.3

Remarks – Results: The notified chemical was found not to be biodegradable under the test conditions as at least 60% of the TOC in a 10-day window within 28-day period of the test was not attained.

In the abiotic control containing the notified chemical and poisoned test medium, no significant degradation was noted at the end of the 28-day exposure period.

In the toxicity control containing both the notified chemical and the reference item sodium benzoate no inhibitory effect on activated sludge microorganisms was observed.

In the procedures controls, the reference item was degraded by an average of 84% by exposure day 14, thus confirming suitability of the activated sludge (>60% degradation by day 14). At the end of the test (day 28), the reference item was degraded by an average of 94%.

CONCLUSION: The notified chemical cannot be classed as ready biodegradable.

TEST FACILITY: RCC Ltd (2003y)

8.1.2. Bioaccumulation

Based on the low logPow of 2.3, the notified chemical is unlikely to bioaccumulate.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	The notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test -96-Hour Static Test. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish-96-Hour Static Test.
Species	Zebra Fish *(Brachydanio rerio)*
Exposure Period	96 hours
Auxiliary Solvent	None.
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Seven fish were used for each treatment and the control. Since the test item contains two different isomers, five Water Accommodated Fractions (WAFs) were tested. These five individual mixtures (supersaturated dispersion of the test substance) with loading rates of 1.0, 2.2, 4.6, 10 and 22 mg/L were prepared by mixing the test substance into the test water as homogenously as possible by ultrasonication for 15 minutes, intense stirring at room temperature in the dark for 96 hours, and membrane filtering. The undiluted filtrate containing a maximum concentration of dissolved test substance was used as a test medium and the concentration determined by HPLC. The test media were clear solutions throughout the entire test duration. Observations for mortality, abnormal behaviour and appearance of the fish were performed at 3.5, 24, 48 72 and 96 h. Water quality measurements (pH, dissolved oxygen and temperature) were within acceptable limits throughout the test.

RESULTS

Loading rate mg/L	*Mean measured concentration*	*Number of Fish/replicate*	*Mortality*				
			3.5 h	*24 h*	*48 h*	*72 h*	*96 h*
Control		7	0	0	0	0	0
1.0	n.a.	7	0	0	0	0	0
2.2[#]	n.a.	7	0	0	0	0	0
4.6	2.7	7	0	0	0	0	0
10	4.6	7	2	6	6	7	7*
22	5.5	7	4	7	7	7*	7*

*number of dead fish plus number of fish with visible abnormalities.
[#]One test fish showed symptoms during the test. However, these symptoms are considered not to be caused by the test item (fish may be injured during insertion of the test fish).
n.a.: not analysed.

LC50	3.5 mg/L at 96 h (CI: 2.7-4.6 mg/L) based on mean measured concentration.
NOEC	2.7 mg/L at 96 h based on mean measured concentration
Remarks – Results	The LC50 was calculated by Moving Average Interpolation (MAI). The LC50s at the observation after 72 and 96 h test duration could not be calculated by Probit Analysis or MAI due to steep concentration effect relationship. Instead, the LC50 values were calculated as the geometric mean value of the two consecutive test concentrations with 0 and 100% mortality and the 95% confidence intervals for the LC50 as the test concentration with 0 and 100% mortality.

At the end of the test 79, 94 and 98% of the initially measured concentrations were found at the loading rates of 4.6, 10 and 22 mg/L, respectively

CONCLUSION The notified chemical is toxic to *Brachydanio rerio*.

TEST FACILITY RCC Ltd (2003z)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE 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	HPLC
Remarks – Method	Two replicates of ten Daphnia each were used for each test concentration and control. The preparation of the WAFs was performed in a similar manner to the fish toxicity test in section 8.2.1. The analytically measured test item concentrations in the test media samples (loading rates 0.46, 1.0, 2.2, 4.6 and 10 mg/L) amounted to 0.39, 0.76, 1.8, 4.0 and 4.9 mg/L at the start of the test. The test media were clear solutions throughout the entire test duration. The test item was stable over the test period. The immobility of the Daphnia was determined visually after 24 and 48 h of exposure. Water quality measurements (pH, dissolved oxygen and temperature) were within acceptable limits throughout the test.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Loading rate	*Actual*		*24 h*	*48 h*
Control	-	20	0	0
0.46	0.42	20	0	1
1.0	0.76	20	16	20
2.2	1.8	20	13	16*
4.6	3.9	20	14	20
10	5.0	20	19	20

* The remaining 4 Daphnia were not immobile but already affected

LC50	0.68 mg/L at 48 h (CI: 0.46 – 1.0 mg/L) based on loading rate 0.56 mg/L at 48 h (0.42–0.76 mg/L) based on mean measured concentration.
NOEC	0.42 mg/L at 48 h based on mean measured concentration.
Remarks – Results	The 24 h and 48 h EC50 could not be calculated by Probit Analysis or Moving Average Interpolation due to the steep concentration-effect relationship. The EC50s were determined by the linear interpolation between log-concentrations and % immobility.

CONCLUSION The notified chemical is very toxic to *Daphnia magna*.

TEST FACILITY RCC Ltd (2003aa)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range Nominal	1.0 - 100 mg/L
Concentration Range Actual	0.95 – 6.0 mg/L
Auxiliary Solvent	None.
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	The test consisted of three replicates per test concentration and six replicates of the control. The samples were continuously illuminated with fluorescent tubes. The preparation of the WAFs was performed in a similar manner as the fish test above. The analytically measured test item concentration in the test media samples (loading rates 1.0, 3.2, 10, 32 and 100 mg/L) amounted to 0.95, 2.9, 5.0, 4.4 and 6.0 mg/L at the start of the test. The test media were clear solutions throughout the entire test duration. pH and temperatures were within acceptable limits throughout the test.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L at 96 h*	*mg/L at 96 h*	*mg/L at 96 h*
>6.0	Not determined.	>6.0	0.53

Remarks – Results	The EC50 values for the biomass and the growth rate after 72 hours test duration could not be determined since the inhibition of growth at the loading rates 3.2 to 100 mg/L was below 50%. At the loading rates of 10 to 100 mg/L, the inhibition of growth rate was about 10 to 13% and the inhibition of biomass amounted to about 30 to 38%. No concentration-response relationship was determined. This corresponds to the analytical results which indicate that the saturation concentration of the test item in test water was reached at these loading rates and resulted in less than 50% inhibition of growth rate and biomass. The biological results were related to the mean measured concentrations of the test substance. The measured concentration of the notified chemical was decreased to values below the limit of quantitation of 0.23 mg/L after 72 h. This decrease appears to be due to photolytic degradation of the notified chemical as a result of the intensive irradiation. At the end of the test (96 h) h, the mean measured concentrations were reduced to approximately 50% of the initially measured concentration
CONCLUSION	The notified chemical is considered not to be toxic to *Scenedesmus subspicatus* up to the limit of its water solubility.
TEST FACILITY	RCC Ltd (2003ab)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 87/302/EEC, Part C.11, Activated Sludge Respiration Inhibition Test, 1988.
Inoculum	Aerobic activated sludge from a wastewater treatment plant (ARA Ergolz II, Fullinsdorf, Switzerland) treating predominantly domestic wastewater.
Exposure Period	3 hours
Concentration Range Nominal	6.3 - 100 mg/L
Remarks – Method	Nominal concentrations of the notified chemical at 6.3, 12.5, 25, 50, and 100 mg/L were used in the test. In addition, two controls and 3 different concentrations of the reference item 3,5-dichlorophenol (5, 16 and 50 mg/L) were tested in parallel.
RESULTS	
IC50	> 100 mg/L
NOEC	> 100 mg/L
Remarks – Results	Up to and including the concentration of 100 mg/L, the notified chemical had no significant inhibitory effect (<15%) on the respiration rate of activated sludge after the incubation period of 3 hours. The saturation concentration (water solubility limit of the notified chemical under the present test conditions) was reached and no significant inhibition was observed after 3 hours contact time. The 3 h EC50 for the reference was within the recommended range of 5-30 mg/L confirming the suitability of the activated sludge.
CONCLUSION	The notified chemical is not considered inhibitory to sewage microorganisms.
TEST FACILITY	RCC Ltd (2003ac)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is slightly volatile and loss to the atmosphere is unlikely to occur from the aquatic environment. It is considered not readily biodegradable (0% after 28 days in a closed bottle test). It is slightly soluble in water (9.9 mg/L) and is hydrolytically stable at pH 4, 7 and 9. It has a logPow of 2.3 and a logKoc of 2.02 indicating that it is unlikely to bioaccumulate or to bind tightly to organic matter in soil.

Most of the notified chemical will be bound to paper and its fate will be dictated by paper disposal trends. The 3 main routes of paper disposal are landfill, incineration and recycling. Recent literature suggests that current paper recycling rates in Australia are 70-92% (Australian Environmental Review, 2001). Consequently, most of the paper containing the notified chemical would be recycled.

Paper recycling is carried out in paper mills, where it is likely that at least primary sedimentation occurs, with some facilities also having biological treatment facilities. Therefore, in these facilities it is expected the notified chemical will partially partition into sludge at the usual waste treatment pH, and eventually be disposed of in landfill with other waste sludge. While the water solubility is relatively low, the fat solubility is also low and it can be assumed that about 50% will stay in the water column. It is anticipated that prolonged residence in an active landfill will eventually degrade the notified chemical contained in sludge or in papers disposed of directly through normal garbage.

Following its use in Australia, it is assumed that 50% of notified chemical will eventually be released into the aquatic environment as a result of the paper recycling process. A calculated worst-case scenario daily PEC in the sewer effluent is 1.7 µg/L. In calculating the PEC, the following were assumed: (1) usage of the maximum import volume is evenly distributed over a 365-day period; (2) usage is nationwide, with a population of 20 million contributing 200 L of water per person per day to the sewer, and (3) there is no adsorption or degradation in the sewer prior to release.

Using the SIMPLETREAT model for modelling partitioning and losses in sewage treatment plants (European Communities, 2003), the percentage removal from solution by STP approximates 0% through volatilisation, 2% adsorption in sludge, and 0% biodegraded. This is based on the Henry's Law Constant (log H) of 5.5 x 10^{-3}, logK_{ow} of 2.3 and no ready biodegradability. Hence, approximately 98% of the inflow concentration of the notified chemical may potentially remain in solution, passing through the STP.

Based on the respective dilution factors of 1 and 10 for rural areas and coastal discharges of effluents, the PECs of the notified chemical in rural areas and coastal water may approximate 1.6 and 0.16 µg/L, respectively.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 0.34 mg/kg (dry wt), assuming 2% attenuation in sludge during the STP process. This is based on the assumption that 0.1 tonne of biosolids is generated for each ML of STP effluent and the consumption of 4000 ML/day for total population per year (2% x 2.5 tonnes/4000 x 0.1 x 365 = 0.34 mg/kg). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1000 kg/m^3 and a soil mixing zone of 0.1 m, the concentration of the notified chemical may approximate 0.034 mg/kg in the applied soil, assuming accumulation of the notified chemical in soil for 10 years under repeated biosolids application.

The effluent re-use (eg. irrigation purposes) concentration of the notified chemical may potentially approximate 1.6 µg/L, assuming 98% remains in solution during the STP process. 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 0.1 m of soil (density 1000 kg/m^3).

Using these assumptions, irrigation with a concentration of 1.6 µg/L may potentially result in a soil concentration of approximately 160 µg/kg assuming accumulation of the notified chemical in soil for 10 years under repeated irrigation.

The PEC values are summarised below:

Sewage effluent/coastal city = 0.16 µg/L
Sewage effluent/rural areas = 1.6 µg/L.
Soil concentrations after 10 years application of biosolids = 34 µg/kg
Soil concentrations following 10 years irrigation with effluent = 160 µg/kg.

Incineration of the waste paper will destroy the notified chemical with the generation of water vapour and oxides of carbon.

Except for paper recycling, the notified chemical is not expected to enter the aquatic environment. In any case, from the $logP_{ow}$ of 2.3, the substance is not expected to bioaccumulate.

9.1.2. Environment – effects assessment

The results of the ecotoxicological data indicate that the notified chemical is very toxic to aquatic life. The most sensitive species is *Daphnia magna*, where the acute EC50 is 0.56 mg/L.

Organism	***Duration***	***Endpoint***	***Concentration (mg/L)***
Zebra fish (*Brachydanio rerio*)	96 h	LC50	3.5
		NOEC	2.7
Waterflea (*Daphnia magna*)	48 h	EC50	0.56
		NOEC	0.42
Alga (*Scenedes-mus subspicatus*)	72 h	E_bC50	>6.0
		E_rC50	>6.0
		NOEC	0.53
Sewage micro-organisms	3 h	EC50	>100

The Predicted No Effect Concentration (PNEC) is 5.6 µg/L, using a safety factor of 100, and the lowest acceptable acute 48 h EC50 for *Daphnia magna* of 0.56 mg/L.

9.1.3. Environment – risk characterisation

Location	**PEC (µg/L)**	**PNEC (µg/L)**	**Risk Quotient (RQ)**
Australia-wide STPs			
Ocean outfall	0.16	5.6	0.03
Inland river	1.6	5.6	0.3

The risk quotients indicate an acceptable risk (Q<1) for both marine and fresh water organisms.

Given the diffuse and widespread use of the ink product, the concentration of the notified chemical in the aquatic compartment is likely to be low. Furthermore, the low Q values indicate that there is unlikely to be an environmental risk to the aquatic compartment.

It is expected that any waste generated during use will be disposed of by incineration or to landfill. In landfill the notified chemical contained in sludge or in papers will degrade slowly via biotic or abiotic processes. Therefore, environmental risk from the reported use pattern of the notified chemical is likely to be low.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The imported notified chemical is a fine powder and will be used at <1% in liquid coating formulations. Exposure during transport and storage would only occur through accidental breaching of the transport containers containing the notified chemical.

Based on the log Pow = 2.3 and MW < 400, the dermal permeability coefficient (Kp) is estimated as 1.6 x 10^{-3} cm/hour (EPA, 1992). This indicates that there will be dermal absorption of the notified chemical. In the absence of other information, dermal absorption must be assumed to be 100% and potential dosages must be assumed to be actual dosages (EC, 2003).

Exposure during formulation of coatings

There is potential for dermal, ocular and inhalation exposure to workers during the manual weighing and transfer of the notified chemical into the formulation tank, especially if dust is produced, as all of the particles are in the inspirable range, and 18% are in the respirable range. Local exhaust ventilation is available for weighing and addition to the tank and PPE (gloves, overalls, disposable dust mask and face shield) would be worn. After addition of the chemical to the mix, the lid is replaced and the remainder of the formulation and filling process occurs within a closed system. EASE (UK HSE, 1997) modelling was carried out to estimate the potential dermal and inhalation exposure of formulation workers to the notified chemical. The model is a conservative one and may overestimate exposure, and it estimates exposure in the absence of personal protective equipment. Exposure of up to 0.1 mg/cm^2/day of the notified chemical was predicted on the basis of non-dispersive use, direct handling and intermittent dermal contact. Using the area of the hands (840 cm^2) and 70 kg body weight, this is 1.2 mg/kg bw/day. Additional potential exposure through inhalation during dry manipulation was estimated at up to 0.093 mg/kg bw/day with local exhaust ventilation, and 0.93 mg/kg bw/day in the absence of local exhaust ventilation, using 1.3 m^3/hour respiration, 1 hour/day exposure and 70 kg average bodyweight. Combined dermal and inhalation exposure is potentially up to 1.3 mg/kg bw/day with local exhaust ventilation, and 2.1 mg/kg bw/day in its absence.

Exposure during use of coatings

A range of equipment may be used for application of the coatings, depending on the type of process and the scale of use. The NICNAS PEC assessment of N-vinyl pyrrolidone (NICNAS, 2000), used in similar processes, identified a variety of control measures in use in different companies. At many sites, the coating processes are highly automated, although some sites contain less automated equipment and use fewer engineering controls. Once the chemical is incorporated into coatings, dermal or ocular exposure could occur during charging of the coating machines, and during cleaning processes. Unless aerosols are generated, inhalation exposure during coating use is expected to be very low because of the high boiling point and estimated low vapour pressure of the notified chemical, however aerosols could be generated during addition to machines.

Using the upper level of 1% notified chemical in coatings, and skin area of 840 cm^2 (both hands), the maximum worst case dermal exposure to the notified chemical in coatings predicted by EASE is 8.4 mg/day, or 0.12 mg/kg bw/day, assuming a body weight of 70 kg and intermittent contact with the formulation. Inhalation exposure would be expected only if aerosols are formed, and may be up to 0.13 mg/kg bw/day in a scenario where local exhaust ventilation is absent, based on 1 h/day exposure. Combined dermal and inhalation exposure is predicted to be up to 0.25 mg/kg bw/day.

The notifier has stated that coating workers and laboratory personnel will wear personal protective equipment to protect skin and eyes from exposure to the coatings, some of which contain sensitisers. Therefore the amount of dermal contact predicted by the EASE model would be an overestimation. Similarly the potential for inhalation exposure is reliant on the formation of aerosols of the formulation being used for coating.

Once the coatings have been applied and cured, the notified chemical will not be available from handling the substrate, as it will be consumed and/or become immobilised through the curing process.

9.2.2. Public health – exposure assessment

The public is not expected to come into contact with the notified chemical or coatings containing it, unless exposed through a transport accident. No exposure is expected from contact with the final coated articles, as the chemical and/or its decomposition products will be bound within the substrate.

9.2.3. Human health – effects assessment

Some discomfort was observed in mice following acute oral exposure, but there were no deaths. No adverse effects were noted in the acute dermal toxicity or the dermal irritation study. No evidence of sensitisation was seen in the LLNA study. There was some irritation to the eye of rabbits, probably due to the notified chemical rather than mechanical irritation, as corneal opacity was seen in addition to conjunctival effects.

The notified chemical caused chromosomal aberrations in Chinese Hamster V79 cells. However, genotoxicity was not observed in the Ames test or an in vivo mouse erythrocyte micronucleus test.

In the 28-day repeat dose toxicity study, a NOAEL of 5 mg/kg bw/day was determined, based on nephrotoxic effects. The notified chemical was lethal to 65% of mice at 160 mg/kg bw/day, and 15% of mice at 100 mg/kg bw/day, with nephrotoxicity identified as a likely cause of death in some mice. Nephrotoxic effects were seen in many mice receiving 50 mg/kg bw/day or more, and persisted after the 2-week recovery period. Adaptive changes were seen in the livers of mice treated with any dose level, and thus no NOEL could be determined. Adverse effects to the upper digestive tract (mainly gastric erosions) were thought to be a portal-of-entry effect. Animals in the 100 and 160 mg/kg bw/day groups were in very poor health overall, exhibiting clinical signs of discomfort, lower food intake and weight loss. This poor health was further supported by lymphoid and splenic atrophy, cortical hypertrophy of the adrenal gland and adverse effects on the reproductive system.

Based on this result, the notified chemical is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004). The appropriate risk phrase is:

R48/22: Danger of serious damage to health by prolonged exposure if swallowed.

The notified chemical will be imported as a powder with respirable fraction (<10 μm): 18.58%; inspirable fraction (<100 μm): 100%; Mass Median Diameter: 16.8 μm. Given that inhalation exposure is possible, and in the absence of any toxicological evidence to the contrary, the notified chemical is also classified as a chronic inhalation hazard. The appropriate risk phrase is:

R48/20: Danger of serious damage to health by prolonged exposure if inhaled.

As the notified chemical is likely to be absorbed through the skin (see section 9.2.1), it also classified as a chronic dermal hazard. The appropriate risk phrase is:

R48/21: Danger of serious damage to health by prolonged exposure to the skin.

9.2.4. Occupational health and safety – risk characterisation

The notified chemical is imported as a powder of small particle size that is incorporated in coating formulations. In preparation of the coating formulations, there is potential for both dermal exposure and inhalation exposure to the notified chemical in powder form. Combined dermal and inhalation exposure was estimated using the EASE model as up to 1.3 mg/kg bw/day with local exhaust ventilation, and 2.1 mg/kg bw/day in its absence. Based on this EASE estimate and the NOAEL of 5 mg/kg bw/day for nephrotoxic effects after repeated exposure, the margin of exposure (MOE) would be 3.8 if local exhaust ventilation is used during formulation processes, and 2.4 in absence of local exhaust ventilation. The extent of potential dermal, ocular and inhalation exposure is reduced by the use of engineering controls and PPE, described as being standard in formulation and use of coatings. The use of full respiratory protection and atmospheric monitoring are recommended in addition to these standard procedures, given the

low NOAEL of the notified chemical. These precautions should reduce exposure to low levels, and thus the MOE should be acceptable when the recommendations are followed.

In the end-use of the formulated coatings there is potential for dermal and ocular exposure to the notified chemical in solution, and potential for inhalation exposure if aerosols are formed. Combined dermal and inhalation exposure (up to 0.25 mg/kg bw/day) could lead to a MOE of 20 in the absence of sufficient ventilation. Accidental spillage could also lead to worker exposure. As stated above, the EASE model generally overestimates contact, and this is a worst-case estimate, for an open system, and in the absence of sufficient ventilation and PPE.

Based on available animal testing, the acute effects of the chemical are expected to be low.

9.2.5. Public health – risk characterisation

The public is not expected to have significant exposure to the notified chemical or coatings containing it. The public will have contact with articles with cured coatings containing the chemical, but it will be immobilised in these media. The possibility of public contact with accidentally spilt chemical is considered low. Because of low exposure, the public health risk is considered low.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. The classification is Harmful Xn and labelling details are:

R48/20: Danger of serious damage to health by prolonged exposure if swallowed.
R48/21: Danger of serious damage to health by prolonged exposure to the skin.
R48/20: Danger of serious damage to health by prolonged exposure if inhaled.

and

As a comparison only, the classification of notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) 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***
Specific target organ systemic toxicity	2	May cause damage to the kidneys and other organs through prolonged or repeated exposure.

The notified chemical is categorised as **Chronic I** based on *Daphnia magna* toxicity data and the substance is not readily biodegradable.

10.2. Environmental risk assessment

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

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is High Concern to occupational health and safety under the conditions of the occupational settings described as atmospheric monitoring is not routinely conducted and full respiratory protection is not employed during formulation of the coatings. During use of the coating products containing the notified chemical there may be High Concern if there is a lack of adequate ventilation.

10.3.2. Public health

There is No Significant Concern to public health when used in cured coatings.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:
  - Xn: R48/20/21/22 Harmful: Danger of serious damage to health by prolonged exposure by inhalation, in contact with the skin and if swallowed.

- Use the following risk phrase for products/mixtures containing the notified chemical:
  - ≥ 5.0%: Xn: R48/20/21/22 Harmful: Danger of serious damage to health by prolonged exposure by inhalation, in contact with the skin and if swallowed.

- The following safety phrases should appear on the MSDS and label for the notified chemical and for formulations which are classified based on the notified chemical:
  - S22 Do not breathe dust
  - S24 Avoid contact with skin
  - S36 Wear suitable protective clothing
  - S37 Wear suitable gloves
  - S38 In case of insufficient ventilation, wear suitable respiratory equipment

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - For formulation, local exhaust ventilation should be used in weighing and mixing areas, to minimise exposure to the notified chemical as a powder.
  - For both formulation and coating operations, the process should be enclosed as much as possible to reduce dermal exposure and the possibility of exposure to aerosols.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced or in products:
  - In handling notified chemical, avoid spills and dust generation.
  - In handling coatings containing the notified chemical, avoid spills, splashes or aerosol generation that would increase exposure.
  - Avoid direct handling of the notified chemical and products where possible

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced or in products:
  - Full respiratory protection capable of filtering out respirable particles, if exposure to dust is likely
  - Gloves
  - Protective clothing
  - Safety eye protection

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

- Atmospheric monitoring should be conducted by employers to measure workplace concentrations during formulation of coatings, using the notified chemical.

- 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 NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- Highly toxic to aquatic organisms. Do not allow material or contaminated containers to enter drains, sewers or water courses

Disposal

- The notified chemical should be disposed of by incineration, landfill or recycling

Emergency procedures

- In case of spill, dampen down powder and avoid dust. Scoop into marked containers for disposal as waste

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act:
  - if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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