File No: STD/1261

November 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

1,2-Cyclohexanedicarboxylic acid, calcium salt (1:1), (1R, 2S)-rel-

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

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

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

Street Address:	334 - 336 Illawarra Road MARRICKVILLE NSW 2204, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

TABLE OF CONTENTS

FULL PUBLIC REPORT

1,2-Cyclohexanedicarboxylic acid, calcium salt (1:1), (1R, 2S)-rel-

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Walk Off Mats Asia Pacific P/L (ABN 14 002 708 830)
Unit7/95 O'Sullivan Beach Rd
LONSDALE SA 5160

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
US TSCA
EU ELINCS
US FDA

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Hyperform HPN 20
EXP-20
Experimental 12894-58
Experimental 11591-54
Experimental 12341-68
Experimental 11214-70
Cis-hexahydrophthalic acid, calcium salt

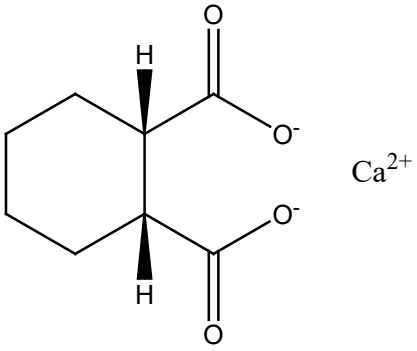
CAS NUMBER
491589-22-1

CHEMICAL NAME
1,2-Cyclohexanedicarboxylic acid, calcium salt (1:1), (1R, 2S)-rel-

OTHER NAME(S)
None.

MOLECULAR FORMULA
$C_8H_{12}O_4.Ca$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
212.26

ANALYTICAL DATA
A reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY 99.5%

HAZARDOUS IMPURITIES
None.

NON HAZARDOUS IMPURITIES (>1% by weight)
None.

There is one impurity at < 0.5%: Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid disodium salt

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Point	> 360°C	Measured
Boiling Point	Not tested	
Density	1670 kg/m^3 at 20°C	Measured
Vapour Pressure	< 2 × 10^{-7} kPa at 25°C	Measured
Water Solubility	0.296 g/L at 20 ± 0.5°C	Measured
Surface Tension	70.4 mN/m at 22°C	Measured
Hydrolysis as a Function of pH	$t_{½}$ y > 1 at pH 4, 7 & 9	Measured
Partition Coefficient (n-octanol/water)	log P_{ow} = -2.56.at 22.2 ± 0.5°C	Measured
Adsorption/Desorption	log K_{oc} <1.25 at 30°C	Measured
Dissociation Constant	Dissociates at a level of 72.7% in deionised water.	Measured
Particle Size	Inhalable fraction (<100 μm): 12.3% Respirable fraction (<10 μm): 3.47%	Measured
Flash Point	Not determined	
Flammability	Not highly flammable	Measured
Autoignition Temperature	333°C	Measured

Explosive Properties	Not explosive	Estimated

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

Reactivity
Not predicted to be reactive.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in 13.3 kg fiber drums, and/or 4.5 and 9 kg bags.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1 - 10	1 - 10	1 - 10	1 - 10	1 - 10

PORT OF ENTRY
Brisbane, Melbourne and Sydney.

IDENTITY OF MANUFACTURER/RECIPIENTS
A partial list of expected Milliken Chemical/WOM customers would include: Qenos, Basell, Guilda and Parmalat.

TRANSPORTATION AND PACKAGING
Likely to be transported mainly by road in 13.3 kg fiber drums, and/or 4.5 and 9 kg bags.

USE
Additive for polyolefin plastic articles designed as a non-dispersive crystallisation modifier.

OPERATION DESCRIPTION
The notified chemical can be added directly in the plastic resin manufacturing process or can be added to a concentrated masterbatch. In each case either the chemical itself or masterbatch pellets are added to a hopper which feeds the mixing chamber of an extruder or injection moulder. The final hot articles or extruded product (eg films) are allowed to cool before automated packaging.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and storage	≤ 5	≤ 8 hours/day	≤ 230 days per year
Equipment maintenance	≤ 5	≤ 8 hours/day	≤ 230 days per year
Manufacture	≤ 5	≤ 8 hours/day (5 minutes to empty drum)	≤ 230 days per year
QC testing	≤ 5	≤ 8 hours/day	≤ 230 days per year

Workers involved in manually adding the notified chemical to a hopper or mixing chamber are potentially exposed to dust. Inhalation exposure is expected to be low given the low level of inspirable and respirable particles and the limited time required for manual addition. However, local exhaust ventilation and respiratory protection are commonly employed. Once the notified chemical is added to the extruder or moulding machine the process is enclosed and exposure is unlikely. Any fumes generated from the hot plastic are vented via

scrubbers to the atmosphere. Extruders and injection moulders are usually placed in areas with good general ventilation to control heat build up in the workplace. Dermal and ocular exposure to the notified chemical is possible during additions and is controlled by the use of gloves and goggles. Workers involved in cleaning and maintenance are potentially exposed to dust but should respiratory protection is expected.

Once in the final polyolefin, the notified chemical is encapsulated and at a low concentration of < 0.25% in products so that exposure to workers is minimal. Masterbatch pellets contain the notified chemical at up to 66% but the chemical is encapsulated and unlikely to migrate from the matrix.

6.1.2. Public exposure

The public should only come in contact with the notified chemical in finished articles. As the notified chemical does not appreciably migrate from the plastic in which it is contained, public exposure should not occur. A study was conducted on migration of the notified chemical from low density polyethylene (LDPE) (Milliken, 2005). Migration conditions were 100°C for 2 hours either followed by 40°C for 238 hours or not. Levels of 0.0002 mg/in^2 were observed in controls and in samples extracted with 10 – 95% ethanol. Using 3% acetic acid as the solvent, levels were 0.0014 mg/in^2 extracted for 2 hours at 100°C and 0.01 mg/in^2 when extracted for a further 238 hours at 40°C. Therefore, migration under conditions to which the public are likely to be exposed can be expected to be low.

6.2. Human health effects assessment

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	oral LD50 > 2000 mg/kg bw low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1000 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days	NOEL = 207 mg/kg bw/day for males; 370 mg/kg bw/day for females
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberrations in human lymphocytes	non genotoxic
Genotoxicity – in vitro mouse lymphoma gene mutation	non genotoxic

The notified chemical was of low acute oral toxicity in rats and adverse effects were not observed at 1000 mg/kg bw/day in a 28-day rat oral repeated dose toxicity study. However, in a 90-day dietary study in rats the NOEL for males was 207 mg/kg bw/day and for females, 370 mg/kg bw/day with the main effect being hypercalcaemia. The notified chemical was not a skin irritant but was a slight eye irritant in rabbits. It was not a skin sensitiser as judged by a negative mouse local lymph node assay and was not genotoxic as judged by negative results in bacterial reverse mutation, human lymphocyte chromosomal aberration and mouse lymphoma gene mutation assays.

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

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

The notified chemical is a powder with > 85% of the particles being above the inhalable size limit of 100 μm. It is imported in small containers which are handled manually for addition of the powder to an injection moulder or an extruder to produce plastic articles or masterbatch plastic pellets for subsequent addition to an extruder (to produce plastic film, for example) or injection moulder to produce plastic articles.

The inhalation exposure of process workers can be estimated using the EASE model (EASE v 2.0, 1997) as a maximum of 0.625 mg/m^3 for inhalable particles and 0.175 mg/m^3 for respirable particles given the percentages of the types of particle listed in Section 4 using the assumptions of dry manipulation and LEV present. The log P_{ow} of < -1 indicates little likelihood of absorption via the respiratory tract (EC, 2003) so it is reasonable to categorise the fraction of the notified chemical which partitions to the workplace air during

manufacturing operations as nuisance dust. The exposure standard suggested by the ACGIH is 3 mg/m^3 for respirable particles (ACGIH, 2001). Thus there is a low risk of adverse respiratory effects for workers manufacturing plastic articles or plastic masterbatches containing the notified chemical.

Although the EASE model predicts dermal exposure at 1 mg/cm^2/day or 840 mg/day (two hands exposed) for process workers or 12 mg/kg bw/day for a 70 kg worker. Skin absorption is unlikely as the log P_{ow} is < -1 (EC, 2003). Based on the NOEL of 207 mg/kg bw/day the margin of exposure is expected to be significantly greater than 100, the level used to account for inter- and intra-species differences. Thus adverse health outcomes are not expected.

Following addition of the notified chemical to an extruder or injection moulder it will become encapsulated and will not be bioavailable. Thus the risk to workers involved in packing off, further processing of masterbatch pellets, QC testing and disposal of waste should be negligible.

6.3.2. Public health

The public will mainly be exposed to the notified chemical as a component of finished articles in which the notified chemical is encapsulated and non-bioavailable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is manufactured overseas and will be transported to Australia in 13.3 kg fiber drums, and/or 4.5 and 9 kg bags. From warehousing locations in Australia, it will be transported to the polyolefin manufactures for production of the final articles for the plastics industry in Australia.

RELEASE OF CHEMICAL FROM USE

Release during use is expected to be minimal, as manufacturing scrap is typically recycled. Any non-recyclable scrap or spilt material is expected to be disposed of to landfill. The notified chemical will not be discharged directly to rivers, lakes or other natural watercourses, and spent packaging containing a small quantity of notified chemical will be disposed of to landfill. Finished articles are expected to be disposed of to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

In landfill, notified chemical arising from spills and as residual within import containers may be mobile due to its relatively high solubility in water. As the notified chemical is readily biodegradable, it is anticipated that the notified chemical will degrade to form simple organic compounds and salts.

Notified chemical associated with finished polyolefin articles is expected to be entrapped within a stable polymer matrix. Eventually, the notified chemical is expected to biodegrade to form simple organic compounds and salts.

7.1.2 Environmental fate

A ready biodegradability test report was submitted, which indicates that the notified chemical can be considered to be readily biodegradable. For the details of the environmental fate study please refer to Appendix C.1.1.

7.1.3 Predicted Environmental Concentration (PEC)

As release to the aquatic environment is not anticipated at any point in the lifecycle of the notified chemical, it is not possible to calculate a Predicted Environmental Concentration.

7.2. Environmental effects assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 >100 mg/L	Not harmful
Daphnia Toxicity	EC50 >100 mg/L	Not harmful
Algal Toxicity	IC50 >100 mg/L	Not harmful
Inhibition of Bacterial Respiration	EC50 >1000 mg/L	Not harmful

All results indicate that the notified chemical is not harmful to aquatic life up to the concentration specified.

7.2.1 Predicted No-Effect Concentration (PNEC)

The PNEC has been calculated as follows, using an assessment factor of 100 as three trophic levels were tested.:

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish)	>100	mg/L
Assessment Factor	100	
PNEC:	>1000	µg/L

7.3. Environmental risk assessment

As it was not possible to calculate a PEC, it is not possible to derive the Risk Quotient (PEC/PNEC). However, a lack of any significant release to the aquatic environment at any stage in the chemical's life-cycle in Australia, combined with its demonstrated lack of ecotoxicity, indicates that under the proposed use pattern, the notified chemical is not expected to pose an unacceptable risk to aquatic organisms or the environment.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

Human health risk assessment

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

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

Environmental risk assessment

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - LEV should be provided at the point of addition of the notified chemical to a hopper or mixing chamber.

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

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

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

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification

This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from an additive for polyolefin plastic articles, or is likely to change significantly;
- the amount of chemical being introduced has increased from 10 tonnes per year, or is likely to increase, significantly;
- if the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point > 360ºC

Method ASTM E537-86
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Determined using Differential Scanning Calorimetry.
Test Facility Safepharm (2006a)

Boiling Point Not determined.

Remarks Not determined due to high melting point.

Density 1670 kg/m^3 at 20ºC

Method OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks Measured with a gas comparison pycnometer.
Test Facility Safepharm (2006a)

Vapour Pressure < 2.0×10^{-8} kPa at 25ºC

Method OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined with a vapour pressure balance between 240-250°C by extrapolation.
Test Facility Safepharm (2006b)

Water Solubility 0.296 g/L at 20 ± 0.5ºC

Method OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method with analysis by Ion Chromatography.
Test Facility Safepharm (2006a)

Surface Tension 70.4 mN/m at 22ºC

Method OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.
Remarks Concentration: 0.290 g/L, ring method, using an interfacial tension balance. The notified chemical is not surface active.
Test Facility Safepharm (2006a)

Hydrolysis as a Function of pH

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

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

Remarks Analysis by Ion Chromatography. Conducted at 50 ± 0.5°C for 5 days.
Test Facility Safepharm (2006a)

Partition Coefficient (n-octanol/water) log Pow = -2.56 at 22.2 ± 0.5ºC

Method OECD TG 107 Partition Coefficient (n-octanol/water).

EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Shake-Flask method with analysis by Ion Chromatography.
Test Facility Safepharm (2006a)

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

Method OECD TG 121 Adsorption - Desorption Using a Batch Equilibrium Method.
EC Directive 92/69/EEC C.19
Remarks HPLC Screening Method. The notified chemical eluted prior to the first reference substance acetanilide. Testing was performed at a neutral pH with the test material in its ionised form only.
Test Facility Safepharm (2006a)

Dissociation Constant Dissociation to ionised form at 72.7% in deionised water.

Remarks Measured by electrical conductivity.
Test Facility Milliken Chemical (Date unkown)

Particle Size 87.7% > 100 µm

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

Range (µm)	*Mass (%)*
< 100 µm	12.3%
< 10.2 µm	3.47%
< 5.4 µm	1.23%

Remarks Sieve used to determine particles > 100 µm; Cascade impactor for particles < 100 µm.
Test Facility Safepharm (2006a)

Flash Point Not determined.

Method EC Directive 92/69/EEC A.9 Flash Point.
Remarks Not determined due to high melting point.

Flammability Not highly flammable.

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks Did not propagate combustion over 200 mm in a preliminary screening test.
Test Facility Safepharm (2006b)

Autoignition Temperature 333°C

Method EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Test Facility Safepharm (2006b)

Explosive Properties Predicted negative.

Method EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks Predicted negative based on structure.
Test Facility Safepharm (2006b)

Dust Explosivity Dust explosion risk: weak

Method ISO (1995) Explosion Protection Systems. Part I: Determination of Explosion Indices of Combustible Dusts in Air ISO 6184/1.
Remarks Sample had a particle size of < 75 µm. Maximum explosion pressure: 7.2 bar. Maximum rate of pressure rise 326 bar/s. Kst value 88 bar.m/s. Minimum explosible concentration: 70 – 80 g/m^3.
Test Facility Milliken (2004)

Oxidising Properties Predicted negative.

Method	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	Structure assessed for chemical groups that would imply oxidising properties, for example, nitrates, metal oxides, hypofluorites, difluoroaminopolynitroaryls, perchlorates, bromates, iodites.
Test Facility	Safepharm (2006b)

Stability Testing Onset of exotherm 237°C.

Method	Specification in Prevention of Fire and Explosion in Dryers, Institute of Chemical Engineers (1990) pp 21 – 23.
Remarks	Thermal Stability, Bulk powder test, 100% of particles < 75 μm. Exothermic reaction commenced at 237°C rising to 578°C.
Test Facility	Milliken (2004)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 92/69/EEC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley
Vehicle	Arachis oil BP
Remarks - Method	No deviations from protocol noted.

RESULTS

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

LD50	> 2000 mg/kg bw (measured); > 2500 mg/kg bw (estimated)
Signs of Toxicity	None.
Effects in Organs	None.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm (2001a)

B.2. Acute toxicity – dermal

Data not provided.

B.3. Acute toxicity – inhalation

Data not provided.

B.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
Number of Animals	3
Vehicle	Water
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No deviations from protocol noted.

RESULTS

Remarks - Results	No Draize scores greater than 0 were recorded in any animal at any time point.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Safepharm (2006c)

B.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	No deviations from protocol noted.

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	1	1 hour	0
Conjunctiva: chemosis	0	0	0			
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	0	0	0			
Iridial inflammation	0	0	0			

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

Remarks - Results — White residual material was noted in two treated eyes at the 1-hour observation time.

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

TEST FACILITY — Safepharm (2006d)

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

TEST SUBSTANCE — Notified chemical

METHOD

Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil (4:1)
Remarks - Method	No deviations from protocol noted.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1878	
5	1946	1.04
10	1870	1.00
25	967	0.51
Positive Control (05/07/2005)		
α-hexylcinnamaldehyde		
5		2.24
10		1.94
25		4.76

Remarks - Results — No deaths and no signs of systemic toxicity were recorded.

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

TEST FACILITY Safepharm (2006e)

B.7. Repeat dose toxicity
7.1 28-Day Repeated Dose Oral Toxicity Study

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).
Japanese Chemical Substances Control Law 1987
OPPTS 870.3050, Repeated Dose 28-day Toxicity Study in Rodents.

Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Propylene glycol
Remarks - Method	Minor deviations from protocol were deviations from the minimal level of relative humidity and the parathyroids from one high dose male and one control female being unavailable for histopathology.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5/sex	0	1 male
low dose	"	50	
mid dose	"	150	
high dose	"	1000	
control recovery	"	0	
high dose recovery	"	1000	

Mortality and Time to Death
1 male was killed in extremis due to a procedural error.

Clinical Observations
Incidental signs were non dose related and were not toxicologically significant. Functional observations were unaffected by treatment. No significant changes in food consumption, body weight or body weight gain were observed.

Laboratory Findings – Clinical Chemistry, Haematology
Clinical chemistry: Slightly reduced bilirubin was observed in high dose males; slightly reduced sodium levels in mid and high dose males remained low at the high dose and increased calcium was observed in high dose males and mid and high dose females.
Haematology: Some slight changes occurring only in recovery animals were unlikely to have toxicological significance.

Effects in Organs
A range of incidental macroscopic findings were not dose related and were similar to those occasionally seen amongst rats of this strain and age. Significant organ weight changes were: a slightly higher relative adrenal weight in high dose females and slightly higher relative liver weights in mid and high dose males. One high dose male showed a bilateral moderate multifocal tubular basophilia in the kidneys.

Remarks – Results
The statistically significant changes in clinical chemistry and organ weights were within the normal range for rats of the strain and age used in the study and did not have histopathological correlates. Therefore, the changes were of little toxicological significance. The single kidney effect identified microscopically in a high dose male was judged to be an isolated occurrence.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the slight effects at this dose level.

TEST FACILITY Notox (2005)

7.2 90-Day Repeated Dose Oral (Dietary) Toxicity Study

TEST SUBSTANCE Notified chemical.

METHOD Toxicological Principles for the Safety Assessment of Food Ingredients (November 2003), US FDA, Red Book 2000.

Species/Strain	Rat/Sprague Dawley
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week
Vehicle	None
Remarks - Method	Deviations from protocol dictated by toxicity of the high dose.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	20/sex	0	1 male
low dose	"	37	0
mid dose	"	370	0
high dose	"	1343*	7 males
control (2)	"	0	0
low dose (2)	"	20	0
mid dose (2)	"	207	0

* Reduced to 50% of this from day 22 due to a deterioration in physical condition and deaths. Due to a progressive decline in physical health the high dose male group was terminated on day 37/38.

Mortality and Time to Death

One control male died on day 56 of severe physical injury to the tail unrelated to treatment.

One high dose male died on day 13 and one male was killed in extremis of day 16 and one on day 19. Following reduction of the by 50% from week 3, further high dose males were killed in extremis on days 28, 29, 34, 35 and 36.

Clinical Observations

Red staining on cage tray linings were noted in high dose males from day 7 and on 5 occasions for high dose females. For the high dose females hunched posture was noted on day 18 only and the presence of a mass was noted in one female. More severe effects were seen in the high dose males. The male which died on day 13 had no clinical signs but the male killed on day 16 showed signs of loss of muscle mass, decreased respiration, pilo-erection, lethargy, hunched posture and dehydration and the male killed on day 19 exhibited signs of hunched posture, tip-toe gait and blood in the urine.

Following reduction of the high dose by 50% clinical signs were still evident for males. One male was terminated following signs of lethargy, decreased and laboured respiration and malfunction of the hind limbs on day 28; one male was terminated on day 29 following signs of laboured and decreased respiration, ptosis, pilo-erection, lethargy and hunched posture; one male was terminated on day 34 following signs of tip-toe gait, hunch posture and pallor of the extremities.

A range of other findings at lower dose levels was considered to be of no toxicological significance.

No toxicologically significant changes in functional performance tests or sensory reactivity scores were found.

No significant trend was observed for bodyweight or bodyweight gain in animals treated with the notified chemical and no effect of treatment was observed on food or water consumption or food efficiency.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical chemistry: At week 2 high dose animals had elevated creatinine, males had a statistically significant increase in blood urea and females, calcium levels. High dose males also showed reduced ASAT and inorganic phosphorus which was also reduced at the mid dose.

At week 7 mid dose males exhibited reduced inorganic phosphorus and sodium ions and an increase in triglycerides.

At week 13 high dose females showed an increase in calcium ions and at the 50% reduced high dose, a slight but significant increase in ASAT.

A range of other changes were either adaptive or judged to be incidental.

Haematology: Haematocrit count was reduced for high dose animals at week 2. Reduced erythrocyte counts were statistically significant only for males and reduced haemoglobin only for females. High dose males showed statistically significant increases in mean cell haemoglobin and elevated neutrophil counts were statistically significant only for males. At week 8 there was a slight but statistically significant increase for mean cell haemoglobin concentration and mean cell haemoglobin for high dose females. Some changes to various parameters at lower doses were judged not to be of toxicological significance due to a lack of consistent response.

Urinalysis: Red staining of the cage liners was correlated with blood in the urine. Although this is reported in isolated cases, in three of five high dose (1343 mg/kg bw/day) males at week 3, haemoglobin was observed in the urine and in one male, bilirubin. A substantial amount of haemoglobin was also observed for one high dose female. Sediment analysis revealed the presence of a markedly high number of erythrocytes in 4 of the 5 high dose males examined and 3 high dose females. Also high dose males showed a reduction in micturated urine volume of increased specific activity. Pre-terminal urinalysis revealed the presence of haemoglobin in 5 of 10 mid dose (370 mg/kg bw/day) males. This was also observed in 2 mid dose and 2 high dose females but the toxicological significance was reduced by the observation of one control females showing the same effect. Pre-terminal sedimentation analysis revealed a higher number of erythrocytes in the urine of one mid dose male and one high dose female treated with 672 mg/kg bw/day.

Effects in Organs

Elevated kidney weights were evident in high dose females. A range of other effects on organ weights were not dose related and had no histopathological correlates so were judged not to be of toxicological significance.

The interim deaths of high dose males showed a number of macroscopic abnormalities including enlarged and hydronephrotic kidneys, distended and dark urinary bladders, with a number of animals showing the presence of multiple calculi.

At terminal kill one high dose female showed enlarged hydronephrotic and pale kidneys. Multiple solid masses were evident in the urinary bladder and ureter.

Histopathology:

In the urinary bladder epithelial hyperplasia, with or without associated subepithelial and peripheral inflammation or haemorrhage was observed for high dose animals with the changes being more severe in males. Calculus formation was observed in two males and in two females. No urinary bladder pathology was seen in control, low (2) and mid (2) dose animals.

In the kidneys focal papillary degeneration/necrosis, tubular basophilia and dilatation, pelvic dilatation (hydronephrosis) and associated haemorrhage/congestion was observed in high dose males. Renal pelvic calculi were seen in two males and mineralisation was not otherwise observed in the renal tissue of males. For high dose females, focal hyperplasia of the pelvic/papillary epithelium was observed, frequently in association with renal pelvic calculi. Significant renal pathology was not observed for any of these animals.

Some effects related to generally debilitated condition were generalised hepatocyte enlargement and hepatocyte basophilia correlated with urinary bladder changes as were interstitial and peripheral inflammatory cell infiltrates and reduced secretory content of the vesicles. Also associated with the urinary bladder changes were inflammatory cell infiltrates, oedema and focal haemorrhage in the prostate.

A greater incidence of higher grades of severity of trabecular bone formation was observed in mid dose males.

Acanthosis and hyperkeratosis was seen in the forestomach of 4 high dose males.

Lymphoid atrophy of the thymus was more severe in high dose males and mesenteric lymph nodes were similarly affected.

Remarks – Results

Clinical signs of red staining detected on cage tray liners, later confirmed as blood from urinalysis were attributed to the presence of renal calculi in high dose males. These stones were confirmed to be calcium phosphate. The most plausible reason for the formation of these calculi was the high calcium content of the notified chemical which resulted in hypercalcaemia. An excessive calcium build up in the kidneys and urine, combined with other waste products to form the calculi resulting in hypercalcuria. Several other probable conditions secondary to the urinary tract pathology were observed in the liver, stomach, thymus, mesenteric lymph nodes, seminal vesicles and prostate. The effects in males resulted in severe clinical signs and lead to a reduction of the high dose by 50% and ultimately to early termination of the high dose males.

Treatment related renal and urinary bladder pathology was also seen in high dose females including slight haemopoietic effects, increases in plasma calcium and the presence of haemoglobin and erythrocytes in the urine. One female exhibited renal calculi.

In addition to these changes, increased trabecular bone formation was observed in mid dose males.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 370 mg/kg bw/day in this study for females and 207 mg/kg bw/day for males.

TEST FACILITY	Safepharm (2006f)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	Phenobarbitone/β-naphthoflavone-induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 0 - 5000 µg/plate b) Without metabolic activation: 0 - 5000 µg/plate
Vehicle	DMSO
Remarks - Method	Replicate assay not performed.

RESULTS

Remarks - Results	No significant increase in the number of revertant colonies per plate above the spontaneous level was observed in any strain at any dose level in the absence or presence of metabolic activation. Toxicity assessed as a visible reduction in growth of the background lawn was noted in all tester strains in the absence of S9 fraction at the top dose. No precipitate was noted on the plates at any dose level. Negative controls were within historical limits and positive controls demonstrated the sensitivity of the test.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY	Safepharm (undated).

B.9. Genotoxicity – bacteria: Study 2

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli* WP2*uvr*A
Metabolic Activation System	Phenobarbitone/β-naphthoflavone-induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 0 - 5000 µg/plate b) Without metabolic activation: 0 - 5000 µg/plate
Vehicle	DMSO
Remarks - Method	No deviations from protocol noted.
RESULTS	
Remarks - Results	No significant increase in the number revertant colonies per plate above the spontaneous level was observed in any strain at any dose level in the absence or presence of metabolic activation. Toxicity assessed as a visible reduction in growth of the background lawn was not noted in any strain. Negative controls were within historical limits and positive controls demonstrated the sensitivity of the test.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm (2001b)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 476 In vitro Mammalian Cell Gene Mutation Test. EC Directive 2000/32/EC B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test. US EPA (1998) Health Effects Test Guidelines. OPPTS 870.5300 *In vitro* Mammalian Cell Gene Mutation Test. EPA 712-C-98-221.
Cell Type/Cell Line	Mouse lymphoma L5178Y
Metabolic Activation System	Aroclor 1254 induced rat liver S9 fraction
Vehicle	DMSO
Remarks - Method	No deviations from protocol noted.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000	3 hours	48 hours	10 – 14 days
Test 2	0, 8, 16, 31, 63, 125, 250, 500, 1000	24 hours	"	"
Present				
Test 1	0, 16, 31, 63, 125, 250, 500, 1000	3 hours	"	"
Test 2	0, 16, 31, 63, 125, 250, 500, 1000	3 hours	"	"

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	250	500	None noted	Negative
Test 2	1000	500	"	"
Present				
Test 1	500	No toxicity	"	"
Test 2		"	"	"

Remarks - Results

The acceptance criteria developed by the Mouse Lymphoma Assay Workgroup of the International Workshop on Genotoxicity Testing (Moore et al., 2006) are as follows:

Negative control: MF: 50 – 170 × 10^{-6}; Cloning Efficiency (CE): 65 – 120%; Suspension Growth (SG): 8 – 32.

Positive control: An increase in MF above spontaneous background of at least 300 × 10^{-6} with at least 40% of the induced MF due to small colonies.

The mean mutation frequency (MF) in test 1 was approximately 300 × 10^{-6}, approximately 65 – 150 × 10^{-6} in the absence of S9 with 24-hour treatment (test 2) and 125 – 183 × 10^{-6} for the repeat of the 3-hour treatment in the presence of S9 (test 2).

For the positive controls, MF exhibited by MMS at 10 µg/mL was 1230 × 10^{-6} – S9 and that for MC at 2.5 µg/mL was 1225 × 10^{-6} + S9. In test 2 the MF for MMS at 5 µg/mL – S9 was 935 × 10^{-6} and that for MC at 2.5 µg/mL was 668 × 10^{-6} + S9.

Therefore, this study is considered acceptable although the numbers of small and large colonies (representing large and small chromosomal events, respectively) were not reported.

CONCLUSION

The notified chemical was not genotoxic to mouse lymphoma L5178Ycells treated in vitro under the conditions of the test.

TEST FACILITY

Huntingdon Life Sciences (2001a)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
US EPA (1998) Health Effects Test Guidelines. OPPTS 870.5375 *In vitro* Mammalian Chromosome Aberration Test. EPA 712-C-98-223.

Cell Type/Cell Line: Human lymphocytes.
Metabolic Activation System: Aroclor 1254 induced rat liver S9 fraction.
Vehicle: DMSO
Remarks - Method: The stability of the test substance and test substance in solvent were not determined as part of this study. Analysis of achieved concentration was not performed as part of this study.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*

Absent			
Test 1	400*, 600*, 800*	3 hours	20 hours
Test 2	100, 200, 400*, 600*, 800*	20 hours	"
Present			
Test 1	400*, 600*, 800*	3 hours	"
Test 2	100, 200, 400*, 600*, 800*	3 hours	"

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1		800	Not noted	Negative
Test 2		-	"	"
Present				
Test 1		-	"	"
Test 2		-	"	"

Remarks - Results: The negative controls were within historical limits and the positive controls exhibited the sensitivity of the test system.

CONCLUSION: The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY: Huntingdon Life Sciences (2001b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated Sewage Sludge Micro-organisms
Exposure Period	28 d
Analytical Monitoring	Ion Chromatography
Remarks - Method	The test material, at a concentration of 10 mg C/L, was exposed to activated sewage sludge micro-organisms with culture medium in sealed culture vessels in the dark at 21°C for 28 days. The degradation of the test material was assessed by the determination of carbon dioxide produced. Control solutions with inoculum and the standard material, sodium benzoate, together with a toxicity control were used for validation purposes.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
8	0	8	65
14	27	14	71
22	74	22	78
28	74	28	80

Remarks - Results	The test material attained 74% degradation after 28 days and satisfied the 10-day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation exceeding 10%.
CONCLUSION	The test material can be considered to be readily biodegradable under the strict terms and conditions of the test guideline.
TEST FACILITY	Safepharm (2006g)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-Static EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - Semi-Static
Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	96 h
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	Ion Chromatography
Remarks – Method	Following a preliminary range finding test fish were exposed, in three groups of ten, to an aqueous solution of the test material, at a single concentration of 100 mg active constituent per litre for a period of 96 hours at a temperature of 12.5 - 13.8°C under semi-static conditions, with daily renewal.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
100	94 - 107	30	0	0	0	0	0

LC50	>100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	Analysis of the test media throughout the exposure period showed measured test concentrations to range from 94% to 107% of nominal and so the results are based on the nominal test concentrations only. The test preparations were observed to be clear, colourless solutions through the duration of the test. No sub-lethal effects were observed.

CONCLUSION — The notified chemical is not harmful to fish.

TEST FACILITY — Safepharm (2006h)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE — Notified Chemical

METHOD — OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Water Hardness	122 mg $CaCO_3$/L
Analytical Monitoring	Ion Chromatography
Remarks - Method	Following a preliminary range-finding test, forty daphnids (4 replicates of 10 animals) were exposed to an aqueous solution of the test material at a single concentration of 100 mg active constituent per litre for a period of 48 hours at a temperature of 21.2 – 21.5°C under static test conditions.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
100	101 - 108	40	0	0

LC50	>100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours
Remarks - Results	Analysis of the test preparations at 0 and 48 hours showed measured test concentrations to range from 101% to 108% of nominal value and so the results are based on the nominal test concentrations only. The test preparations were observed to be clear, colourless solutions through the duration of the test.

CONCLUSION — The notified chemical is not harmful to daphnids.

TEST FACILITY — Safepharm (2006i)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE — Notified Chemical

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

Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours

Concentration Range	Nominal: 100 mg/L Actual: 99 - 107 mg/L
Analytical Monitoring	Ion Chromatography
Remarks - Method	Following a preliminary range-finding test, *Pseudokirchneriella subcapitata* was exposed to an aqueous solution of the test material at a single concentration of 100 mg active constituent per litre for a period of 96 hours, under constant illumination and shaking at a temperature of 24±1°C.

RESULTS

Biomass		*Growth*	
E_bC50	*NOE_bC*	*E_rC50*	*NOE_rC*
mg/L at 96 h	*mg/L*	*mg/L at 96 h*	*mg/L*
>100	100	>100	100

Remarks - Results	Analysis of the test preparations at 0 and 96 hours showed measured test concentrations to range from 99 – 107% of nominal and so the results are based on the nominal test concentrations only. All test and control cultures were inspected microscopically at 96 hours. There were no abnormalities detected in any of the control or test cultures. At the start of the test all control and test cultures were observed to be colourless solutions. After the 96 hour test period all control and test cultures were observed to be bright green dispersions.
CONCLUSION	The notified chemical is not harmful to algae.
TEST FACILITY	Safepharm (2006j)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 1000 mg/L
Remarks – Method	Following preliminary range-finding tests, activated sewage sludge was exposed to an aqueous dispersion of the test material at a concentration of 1000 mg active constituent per litre (three replicate flasks) for a period of 3 hours at a temperature of 21°C with the addition of a synthetic sewage as a respiratory substrate. The rate of respiration was determined after 30 minutes and 3 hours contact time and compared to data for the control and a reference material, 3,5-dichlrophenol.
RESULTS	
IC50	>1000 mg/L
NOEC	1000 mg/L
Remarks – Results	Analysis of the concentration, homogeneity and stability of the test material in the test preparations was not appropriate to the Test Guidelines. The reference material gave a 3 hour EC50 value of 11 mg/L. The validation criteria for the control respiration rates and reference material EC_{50} values were satisfied.

CONCLUSION	The notified chemical is not harmful to sewage micro-organisms.
TEST FACILITY	Safepharm (2006k)

BIBLIOGRAPHY

ACGIH (2001) The American Conference of Governmental Industrial Hygienists (ACGIH): Threshold Limit Values for Chemical Substances and Physical Agents and Biological Indices 2001; ACGIH Cincinnati, Ohio.

EASE (1997) v 2.0 UK Health and Safety Executive.

Huntingdon Life Sciences (2001a) Experimental 11214-70 Mammalian Cell Mutation Assay. Report No. KMU 004/013841. Huntingdon Life Sciences Ltd, Cambridgeshire, England (unpublished report submitted by notifier).

Huntingdon Life Sciences (2001b) Experimental 11214-70 In Vitro Mammalian Chromosome Aberration Test in Human Lymphocytes. Report No. KMU 004/013532. Huntingdon Life Sciences Ltd, Cambridgeshire, England (unpublished report submitted by notifier).

Milliken Chemical (Date unknown) Determination of the Dissociation of the Calcium Salt of Cyclohexanedicarboxylic Acid, Russell Harlan, Ph.D., Research & Development Associate, Milliken Chemical, 920 Milliken Road, M-401, Spartanburg, SC 29304 (unpublished report submitted by notifier).

Milliken (2004) Dust Explosibility and Thermal Stability of Experimental 12341-68. Report No. R/4878/0504/NK. Milliken Chemical, 920 Milliken Road, M-401, Spartanburg, SC 29304 (unpublished report submitted by notifier).

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

Notox (2005) Repeated Dose 28-Day Oral Toxicity Study with Experimental 11591-54 by Daily Gavage in the Rat, followed by a 14-Day Recovery Period. Project No. 430594. Notox B V, 's-Hertogenbosch, The Netherlands (unpublished report submitted by notifier).

Safepharm (undated) Experimental 11569-34: Experimental 11569-34: Reverse Mutation Assay "Ames Test" using *Salmonella typhimurium* – Single Experiment. Report No. 656/061. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2001a) Experimental 11214-70: Acute Oral Toxicity in the Rat – Acute Toxic Class Method. Report No. 656/089. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2001b) Experimental 11214-70: Reverse Mutation Assay "Ames Test" using *Salmonella typhimurium* and *Escherichia coli*. Report No. 656/088. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006a) Determination of General Physico-Chemical Properties, SPL Project Number 0656/0279, 27 April 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006b) Determination of Hazardous Physico-Chemical Properties, SPL Project Number 0656/0280, 1 February 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006c) Experimental 11591-54: Acute Dermal Irritation in the Rabbit. Report No. 0656/0281. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006d) Experimental 11591-54: Acute Eye Irritation in the Rabbit. Report No. 0656/0282. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006e) Experimental 11591-54: Local Lymph Node Assay in the Mouse. Report No. 0656/0283. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006f) Experimental 12894-58: Ninety Day Repeated Dose Oral (Dietary) Toxicity Study in the Rat. Report No. 0656/0277. Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006g) Assessment of Ready Biodegradability; CO_2 Evolution Test, SPL Project Number 0656/0314, 24 March 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006h) Acute toxicity to Rainbow Trout, SPL Project Number 0656/0284, 2 May 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006i) Acute toxicity to *Dapnhia magna*, SPL Project Number 0656/0285, 2 May 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006j) Algal Inhibition Test, SPL Project Number 0656/0286, 13 July 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

Safepharm (2006k) Assessment of the Inhibitory Effect on the Respiration of Activated Sewage Sludge, SPL Project Number 0656/0287, 28 April 2006, Safepharm Laboratories Ltd, Shardlow Business Park, Shardlow, Derbyshire, DE72 2GD, UK (unpublished report submitted by notifier).

United Nations (2003) Globally Harmonised System of Classification and Labelling of Chemicals (GHS). United Nations Economic Commission for Europe (UN/ECE), New York and Geneva.