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March 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

12H-Dibenzo[d,g][1,3,2]dioxaphosphocin, 2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-, 6-oxide, lithium salt

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Marubeni Australia Ltd (ABN 000 329 699)
Level 18, 367 Collins St
Melbourne VIC 3000

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:
Names of testing facilities

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Japan ENCS: notified 2004
US/TSCA: notified 2000, listed on TSCA inventory 2001
Canada/CEPA: notified 2004
EU/VIIA: notified 2004
Korea/TCCL: notified 2004, listed on ECL 2005

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
12H-Dibenzo[d,g][1,3,2]dioxaphosphocin, 2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-, 6-oxide, lithium salt

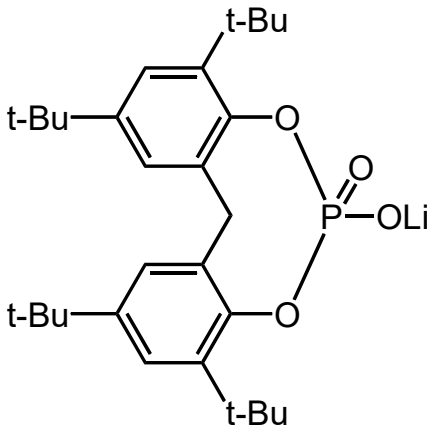
OTHER NAME(S)
2,4,8,10-tetra(tert-butyl)-6-hydroxy-12H-dibenzo[d,g][1,3,2]dioxaphosphocin 6-oxide, lithium salt;
2,2'-Methylenebis(4,6-di-tert-butylphenol) phosphate lithium salt.

MARKETING NAME(S)
ADK STAB NA-71 (powder preparation containing 80-85% of the notified chemical)

CAS NUMBER
85209-93-4

MOLECULAR FORMULA
$C_{29}H_{43}O_4P.Li$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
492.56

SPECTRAL DATA

METHOD UV/visible spectrophotometry
Methanol was used as a solvent with a concentration of 10^{-3},10^{-4},10^{-5} mol/L
λmax = 279 nm, $\varepsilon = 1.97 \times 10^3$
λmax = 271 nm, $\varepsilon = 1.78 \times 10^3$

Infrared (IR) spectrophotometry
Major peaks at 2957, 2868, 1601, 1393, 1364, 880, 787, 1098 cm^{-1}

^1H NMR spectrophotometry (in CD_3OD)
Peaks at 7.26 (2H, d, J = 2.5 Hz; Ph), 7.21 (2H, dd, J = 2.5 Hz and 1.0 Hz; Ph), 4.00 (2H, br-s; CH_2), 1.46 (18H, s; t-Bu), 1.28 (18H, s; t-Bu) ppm.

^{13}C NMR spectrophotometry (in CD_3OD)
Peaks at 149.21 (Ph), 146.71 (Ph), 141.63 (Ph), 134.36 (Ph), 126.02 (Ph), 123.51 (Ph), 36.19 (t-Bu), 36.08 (CH_2), 35.22 (t-Bu), 31.99 (t-Bu), 31.72 (t-Bu) ppm.

Remarks The spectral data were consistent with the structural properties of the notified chemical.
TEST FACILITY Test Facility A (2002)

METHODS OF DETECTION AND DETERMINATION

METHOD HPLC
Remarks Mobile phase: Methanol/water/acetic acid 78/19/3
Detection wavelength: 275 nm
Ambient temperature
Single peak, retention time approximately 6.5 minutes.
TEST FACILITY Test Facility B (2003a)

3. COMPOSITION

DEGREE OF PURITY
> 98%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	Water		
CAS No.	7732-18-5	*Weight %*	< 2

ADDITIVES/ADJUVANTS
None

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a component (80-85%) of a powder preparation (ADK STAB NA-71).

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

Year	*1*	*2*	*3*	*4*	*5*
	1	3	5	10	15

USE
The notified chemical will be used as a nucleating agent and/or a clarifying agent in polypropylene plastics. These plastics will be used to manufacture products such as automotive moulded parts for the interior and exterior of motor vehicles, as well as components of electrical appliances.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
None identified.

TRANSPORTATION AND PACKAGING
The powder preparation will be imported in 10 kg plastic-lined cardboard boxes, stored in a bunded warehouse for less than 1 week, and then transported by road to the plastic manufacture site.

5.2. Operation description

The powder preparation (80-85% notified chemical), plastic powder, filler and other additives will be weighed and added manually into a closed system mixer. The powders will be mixed and the resultant mixture will be fed automatically to a closed preheated extruder, which will produce the plastic pellets. Less than 0.3% of the notified chemical will be present in the pellets. The pellets will be automatically weighed and packed into bulk bags. Laboratory technicians will be involved in sampling and laboratory quality analysis.

During the production of the final plastic articles the plastic pellets will be manually transferred into the open hopper of an injection moulding machine. The pellets will be heated in the closed system moulding machine and injected as a liquid under pressure into moulds to form articles containing up to 0.3% of the notified chemical.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and warehousing	1-2	<8 hours/day	5-7 days/year
Warehousing	2-3	1 hour/day	10-20 days/year
Formulation of plastic pellets	5-10	2-4 hours/day	60-100 days/year
Laboratory technician: sampling and quality analysis	1-2	1 hour/day	60-100 days/year
Cleaning of the mixer, the hopper and floor	1-2	1 hour/day	60-100 days/year
Maintenance of extruder	1-2	1 hour/day	12 days/year
Moulding of finished articles	5-10	2-4 hours/day	60-100 days/year
Maintenance of moulding machinery	1-2	1 hours/day	12 days/year

Exposure Details
Transport and warehousing workers will have low exposure as under normal circumstances, they will only handle sealed packages.

Formulation of plastic pellets
Dermal, ocular and inhalation exposure to the notified chemical is possible when the chemical is weighed and poured into the mixer. The notified chemical is normally weighed into small plastic containers in a booth fitted with an extraction fan. Exposure will be minimised by personal protective equipment (PPE) such as a particle-filter mask, safety glasses, head covering, gloves and overalls. Local exhaust ventilation is present in the weighing and loading areas, as well as the mixers, which are exhausted to dust filter bags. The mixer, the hopper used to enter the powder into the mixer, and the floor around the hopper will be cleaned by a vacuum cleaner. The cleaning workers will wear PPE such as dust masks, safety glasses, gloves and overalls. Laboratory technicians will be involved in quality control of the formulated pellets. The notified chemical is bound within the matrix of the plastic pellets and contact with the notified chemical is therefore not expected. Laboratory technicians will also wear protective equipment such as a laboratory coat, safety glasses and gloves when carrying quality control tests.

Moulding of finished articles
The notified chemical will be present at a concentration of <0.3% and will be encapsulated in pellets. Due to the function of the notified chemical as a nucleating agent, it is expected to be bound within the plastic. Therefore although dermal contact with the pellets will occur during manual transfer, exposure to the notified chemical is not expected at this stage. At the end-use site these pellets will be used to injection mould various articles. Workers will wear gloves and eye protection. Exhaust ventilation is preset to the moulding machines.

5.4. Release

RELEASE OF CHEMICAL AT SITE
There will be no release in Australia due to manufacture as the notified chemical will not be manufactured here.

Release to the environment during shipping, transport and warehousing will only occur through accidental spills or leaks of the polyethylene bag container. This is expected to be minor due to the packaging of the material. Spilt material is expected to be physically contained, collected, and either disposed of if contaminated or repackaged for use.

RELEASE OF CHEMICAL FROM USE
There will be some residual powder left in the empty import bags. This is estimated to be less than 0.1% of the annual import volume. Empty bags and any residuals will be disposed of by incineration or landfill.

During the extrusion process to incorporate the notified chemical into plastic pellets and the production of the final plastic article, waste will be generated by spillage, off-cuts, out-of-specification material and equipment cleaning. This waste accounts for up to 3% of the imported notified chemical and will be collected and disposed of by incineration or landfill.

The process equipment will not be washed between batches. In each batch the first lot of product is discarded. Any spilt material will be collected and placed into sealable containers ready for disposal.
In the end product the notified chemical is incorporated in an inert matrix and will not be released to the environment.

5.5. Disposal

All the solid wastes generated containing the notified chemical will either be disposed of to landfill or by incineration. In landfill the notified chemical will not be mobile and may very slowly undergo abiotic and biotic degradation. Notified chemical that is disposed of by incineration is expected to be thermally decomposed to form various oxides of carbon, phosphorous and lithium.

5.6. Public exposure

The public may come into contact with finished articles containing the notified chemical however because the notified chemical is a nucleating agent it is expected to be bound within the plastic, and no release of the notified chemical from the finished articles is expected.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa White powder

Melting Point/Freezing Point > 360ºC

METHOD	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	No melting point observed below 360°C using the metal block method.
TEST FACILITY	Test Facility B (2003a)

Boiling Point > 360ºC at 101.3 kPa

METHOD	OECD TG 103 Boiling Point. EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	No boiling point was observed below 360°C.
TEST FACILITY	Test Facility B (2003a)

Density 1117 kg/m^3 at 20ºC

METHOD	OECD TG 109 Density of Liquids and Solids. EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Density was determined using a pycnometer, the reference liquid was hexane.
TEST FACILITY	Test Facility B (2003a)

Vapour Pressure 3.37 x 10^{-8} kPa at 25ºC .

METHOD	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Vapour pressure was measured using the effusion method: vapour pressure balance.
TEST FACILITY	Test Facility B (2003a)

Water Solubility 0.39 g/L at 20ºC

METHOD	OECD TG 105 Water Solubility. EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Flask Method. Analytical Method: HPLC. 0.15 g was combined with 100 mL distilled water. After stirring for up to 3 days, and then being allowed to stand for

1 day, a 5 mL aliquot was filtered through a 0.45 µm filtration unit and diluted to 10 mL with methanol, to produce solutions in methanol/water, 50/50 v/v, which were subsequently analysed using HPLC. With respect to the environment, the notified chemical is moderately soluble (Mensink *et al*, 1995)

TEST FACILITY Test Facility B (2003a)

Fat (or n-octanol) Solubility < 0.025 g/100 g Standard Fat at 37 °C

METHOD OECD TG 116 Fat Solubility of Solid and Liquid Substances.

Remarks Analytical Method: UV-VIS. 3-4 mg was combined with 25 g Standard Fat. Undissolved test substance was separated from the saturated fat solution by filtration through a 0.45 µm filtration unit. 1 g aliquots of the filtrate were diluted with tetrahydrofuran, and the solutions were analysed for test substance using UV-VIS. None of the test solutions exhibited absorbances greater than the most dilute concentration standard (2.5 mg/L).

TEST FACILITY Test Facility B (2003a)

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)*	*$t_{½}$ (days)*
4	-	-
7	25	>365 days
9	25	>365 days

Remarks The solubility of T-71 was found to be too low at pH 4 to allow the determination of the hydrolytic half-life under the conditions used.

TEST FACILITY Test Facility B (2003b)

Partition Coefficient (n-octanol/water) log Pow at 22.5°C = 2.50

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

Remarks Analytical Method: HPLC. The test was conducted using only 20% water in the mobile phase as opposed to the minimum of 25% required in the protocol. This error does not impact the scientific integrity of the study because the test substance was retained on the column and eluted within the range of the 6 reference compounds. The test substance eluted between the reference substances Sodium Nitrate and Acetanilide.

TEST FACILITY Test Facility B (2003a)

Adsorption/Desorption – screening test log K_{oc} < 1.25 at ambient temperature.

METHOD OECD 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography.
EC Directive 2001/59/EC C.19 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography

Remarks The test substance eluted between the reference substances Thiourea and Acetanilide.

TEST FACILITY Test Facility B (2003a)

Dissociation Constant No dissociation constant observed between pH 2 and pH 13.

METHOD OECD TG 112 Dissociation Constants in Water.

Remarks Solutions of T-71 were prepared in hydrochloric acid and potassium hydroxide to produce solutions equivalent to pH 2 and pH 13 respectively. These solutions were

examined by UV spectrophotometry. No dissociation constant was observed between pH 2 and pH 13.

TEST FACILITY Test Facility B (2003a)

Particle Size

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

Range (μm)	*Mass (%)*
≤ 2	6.2
2 to 200	93.8
≥ 200	0

Remarks The particle size distribution was determined using a Coulter Counter. The OECD Guideline 110 states that this method should only be used for water insoluble compounds (< 10^{-6} g/L), however the notified chemical has a water solubility of 0.39 g/L. Therefore the results presented here may over-estimate the particle sizes.

The Coulter Counter volume statistics indicate a particle size distribution between 0.7 and 79 μm equivalent spherical diameter. Microscopic examination revealed rectangular crystals of greatly varying size. The MMAD cannot be calculated using this method, however it could be estimated from the measured diameters and the relative density. The proportion of particles with an aerodynamic diameter less than 10μm was estimated to be 25%.

TEST FACILITY Test Facility B (2003a)

Flash Point Not determined.

Remarks The notified chemical is a solid with a low vapour pressure and is therefore not expected to form a flammable air/vapour mixture.

Flammability Limits Not highly flammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks The notified chemical failed to ignite in the preliminary test.
TEST FACILITY Test Facility B (2003a)

Autoignition Temperature > 400°C

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks There was no exothermic reaction observed under the conditions of the test, indicating that the notified chemical does not self-ignite below 400°C.
TEST FACILITY Test Facility B (2003a)

Explosive Properties Not explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks No explosion or reaction was observed when the notified chemical was tested for thermal sensitivity or mechanical sensitivity (shock and friction).
TEST FACILITY Test Facility B (2003a)

Oxidizing Properties Not oxidizing

METHOD EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks In the preliminary tests none of the test piles of the notified chemical burned to completion. Therefore the notified chemical was considered to be non-oxidizing.
TEST FACILITY Test Facility B (2003a)

Reactivity

Remarks Based on the chemical structure and experience of the notifier in use, the notified chemical is predicted to be stable under normal conditions.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral	LD50 > 2000 mg/kg bw, low toxicity
Rat, acute dermal	LD50 > 2000 mg/kg bw, low toxicity
Rat, acute inhalation	LC50 3.11 mg/L/4 hour, harmful
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay	no evidence of skin sensitisation
Rat, oral gavage repeat dose toxicity -28 days.	NOAEL = 250 mg/kg bw/day
Genotoxicity - bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test in human lymphocytes	non genotoxic
Genotoxicity – in vitro mammalian cell mutation assay	genotoxic
Genotoxicity – in vivo mouse micronucleus test	non genotoxic
Genotoxicity – in vivo unscheduled DNA synthesis test	non genotoxic

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD TG 401 Acute Oral Toxicity-Limit test
EC Directive 92/69/EEC B.1 Acute Toxicity (Oral) – Limit Test.
Species/Strain Rat/Wistar strain HanIbm: WIST (SPF)
Vehicle 1% aqueous carboxymethyl cellulose
Remarks - Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 Male	2000 mg/kg bw	0/5
2	5 Female	2000 mg/kg bw	0/5

LD50 > 2000 mg/kg bw
Signs of Toxicity Uncoordinated movements were observed in two females on day 1.
No effect on bodyweight was seen.
No mortality occurred.
Effects in Organs No abnormalities were found at macroscopic post mortem examination.

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

TEST FACILITY Test Facility C (1995a)

7.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity – Limit Test.

	EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Sprague-Dawley CD strain
Vehicle	Arachis oil BP
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 Male	2000 mg/kg/bw	0/5
2	5 Female	2000 mg/kg/bw	0/5

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of dermal irritation.
Signs of Toxicity - Systemic	There were no signs of systemic toxicity. No effect on bodyweight was seen. No mortality occurred.
Effects in Organs	No abnormalities were noted at necropsy.

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

TEST FACILITY Test Facility D (2004a)

7.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 403 Acute Inhalation Toxicity.
EC Directive 92/69/EEC, 93/21/EEC B.2 Acute Toxicity (Inhalation).

Species/Strain	Sprague Dawley rat/ Crl:CD (SD) IGS BR strain
Vehicle	None
Method of Exposure	Oro-nasal exposure.
Exposure Period	4 hours
Physical Form	solid aerosol (particulate)
Particle Size	MMAD = 2.5-4.1μm; Inhalable fraction (<4 μm) = 50-64%
Remarks - Method	No significant protocol deviations reported. The particle size distribution was determined at least three times during each exposure period using the Cascade Impaction method with six impactor stages (9.6, 6.6, 3.5, 1.8, 0.87 and 0.33 μm cut points). A characterisation study was conducted, in which two rats (one male and one female) were exposed to an atmosphere of the notified chemical at a mean achieved concentration of 2.03 mg/l for approximately 4 hours. One animal was found dead during the exposure and the other animal was found dead on Day 1 post-exposure. The results of this study were used to determine the concentration range for the main study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	5 male; 5 female	1.27	1.00	0
2	5 male; 5 female	5.31	1.96	2 (Both male)
3	5 male; 5 female	6.63	5.03	10

LC50	3.11 mg/L/4 hours
Signs of Toxicity	After exposure to the notified chemical hunched posture, piloerection,

	and wet fur was observed in all three dosage groups, although these symptoms could be associated with the restraint procedure. Other abnormalities observed are described below for each dosage group: *Group 1*: Increased respiratory rate was observed in all animals during exposure and up to three days after exposure. Frequent instances of noisy respiration were observed, as well as an isolated instance of red/brown staining around the head. Animals recovered quickly to appear normal from Days 4 to 6 post-exposure. Two males showed reduced bodyweight gain during Week 1 but both had recovered by Week 2. Two females showed almost no body weight gain over the study period. One female showed slight bodyweight loss during Week 2. *Group 2*: One male was found dead 46 minutes post-exposure, and a further male was found dead one day after exposure. Increased respiratory rate in all animals and laboured respiration in some animals observed during and after exposure. Frequent instances of noisy respiration and red/brown staining around the head were also observed after exposure. Isolated instances of sneezing were observed from Day 3 to Day 5 post-exposure. Observations gradually receded in surviving animals such that they appeared normal from Days 8 to 10 post-exposure. Five female animals exhibited a reduced bodyweight gain or slight bodyweight loss during Week 1, but had recovered by Week 2. *Group 3*: Laboured respiration and sporadic cases of increased respiration and decreased respiration were observed during exposure. Two males and one female were found dead at 224 minutes, 230 minutes and 229 minutes during exposure respectively. After exposure the surviving animals showed decreased respiratory rate, laboured respiration, noisy respiration, ataxia, as well as occasional instances of gasping respiration, fur loss and red/brown staining around the snout. Two males and one female were found dead approximately 157 minutes post-exposure. One female and one male animal displayed gasping respiration and prostration and were humanely killed approximately 105 and 162 minutes post-exposure respectively. The remaining two female animals were found dead one day after exposure.
Effects in Organs	The lungs of the animals that survived to the Day 14 necropsy were found to display one or more of the following abnormalities: enlarged, fluid-filled, abnormally dark, pale patches, dark patches. The following abnormalities were found amongst the animals that died or were humanely killed during the study: Lungs – haemorrhagic, fluid-filled, abnormally dark, pale patches; Liver – dark; Kidneys – dark or pale; Stomach – gaseous distension; Small intestine – gaseous distension; Large intestine – gaseous distension.
Remarks - Results	The LC50 value (3.11 mg/L/4 hours) was estimated by Linear Interpolation using analysis software. Due to the nature of the results obtained it was impossible to determine the 95% confidence limits.
CONCLUSION	The notified chemical is harmful via inhalation.
TEST FACILITY	Test Facility D (2006)

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
Number of Animals	3
Vehicle	Distilled water (0.5 mL, used for moistening)
Observation Period	4-hour
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	0	0	0
Oedema	0	0	0	0	0	0

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

Remarks - Results No evidence of skin irritation was observed.

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

TEST FACILITY Test Facility D (2004b)

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-hour
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.33	1	0.33	2	< 72 hours	0
Conjunctiva: chemosis	0	0.33	0	2	< 48 hours	0
Conjunctiva: discharge	0	0.66	0	2	< 72 hours	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	1	< 24 hours	0

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

Remarks - Results	A single application of the test material to the non-irrigated eye of three rabbits produced iridial inflammation (one animal, 1-hour observation) and moderate conjunctival irritation (three animals). Two treated eyes appeared normal at the 48-hour observation and the remaining treated eye appeared normal at the 72-hour observation.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Test Facility D (2004c)

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

TEST SUBSTANCE	Notified chemical
METHOD	OECD 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone:olive oil (4:1); test substance added as suspension.
Remarks – Method	No significant protocol deviations. Doses selected based on maximum practical concentration for pinna dosing.

RESULTS

Concentration	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0%	327.2	
5%	741.9	2.3
10%	483.8	1.5
25%	507.1	1.5
Positive Control		
0%	408.4	
10%	2127.8	5.2
25%	3714.9	9.1
50%	4670.2	11.4

Remarks – Results	Evidence of induction of T-cell proliferation was not observed with the test substance, as the stimulation index was less than three at each of the test concentrations. The stimulation index for the positive control was dose related, with positive responses at all doses, therefore confirming the validity of the assay. There were no deaths and no signs of ill health or toxicity observed during this study. Greasy fur was noted for all control and test animals post-dose from Day 1. This sign had resolved completely in all animals by Day 5. White test substance staining was noted in all animals in the mid dose and high dose groups shortly after dosing from Day 1 or 2 and had resolved by Day 4. In addition, white test substance staining was also noted in all animals in the low dose group on Day 3 only. A loss in bodyweight was recorded for two females in the low dose group, one female in the mid dose group and two females in the high dose group during the study. All remaining animals gained weight during the study.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Testing Facility B (2004a)

7.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Crl:CD (SD) IGS BR rats
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 Dose regimen: 7 days per week; Post-exposure observation period: 14 days
Vehicle	1% methyl cellulose in water
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5 per sex	0	0
II (low dose)	5 per sex	80	0
III (mid dose)	5 per sex	250	0
IV (high dose)	5 per sex	1000	0

Mortality and Time to Death

No mortality was observed during the treatment or recovery phases.

Clinical Observations

Clinical observations were confined to pale faeces noted among animals from all treated groups, together with loose faeces occurring among both sexes receiving 1000 mg/kg bw/day, between Days 3 to 5 of treatment. In addition hair loss was noted from Day 12 in approximately half of the male and female animals receiving 1000 mg/kg bw/day, and a low incidence of post dose salivation, occurring among both sexes, was observed among animals at this dose level during Week 4.

The neurobehavioural screening did not reveal any conclusive treatment related changes that were considered to be indicative of neurotoxicity.

Bodyweight gain and the efficiency of food utilisation were increased for females treated at 250 and 1000 mg/kg bw/day during the 4 week treatment.

Water consumption was higher than control for males, and slightly higher for females receiving 1000 mg/kg bw/day in Week 3 of treatment. During Week 2 of recovery water consumption was slightly lower than control for females and similar to control for males previously treated at 1000 mg/kg bw/day, indicating recovery from the higher water intake noted during Week 3 of treatment.

Laboratory Findings

Haematology

The haematology investigations carried out on Day 29 revealed statistically significantly higher than control mean values for total white cell counts, neutrophils, lymphocytes, basophils, monocytes, large unstained cells receiving 1000 mg/kg bw/day. Assessment of the Day 15 recovery data for females previously treated at 1000 mg/kg bw/day continued to show higher mean values for the white cell parameters, although these differences were due to the high values of two individual females. The individual values for the white cell parameters for the remaining three female recovery animals were similar to control, showing a degree of recovery from the previous effects of treatment. The mean activated partial thromboplastin values were higher than controls (but not statistically significant) for females treated at 1000 mg/kg bw/day, although there was no obvious dose response. At the end of the 4 week period, treatment values were lower than control indicating recovery from the changes previously observed.

Clinical Chemistry

The Day 29 blood chemistry investigations revealed higher mean alkaline phosphate values for males (statistically significant) receiving 250 or 1000 mg/kg bw/day and females (not statistically significant) receiving 1000 mg/kg bw/day. Higher mean alanine and aspartate aminotransferase levels were noted for males receiving 1000 mg/kg bw/day, although this was mainly due to the higher than control values occurring

in 2 male animals for these parameters. Lower than control mean cholesterol levels were noted for females receiving 250 (not statistically significant) or 1000 (statistically significant) mg/kg bw/day and males (not statistically significant) receiving 1000 mg/kg bw/day. Higher mean triglyceride values were seen for both sexes receiving 1000 mg/kg bw/day, when compared with control. Total protein mean values were lower than control among males receiving 250 or 1000 mg/kg bw/day due to lower than control globulin values, which also resulted in slightly higher mean A/G ratio values for males at these dose levels. Among females receiving 1000 mg/kg bw/day lower than control total protein values were noted which were associated with lower albumin values among these females. Assessment of the data for the recovery group animals previously treated at 1000 mg/kg bw/day revealed values that were similar to control indicating recovery from the previous effects of treatment.

Urinalysis
The urinalysis investigations carried out on Day 29 revealed lower than control mean protein values among all treated female groups which followed a dosage related trend, together with marginally higher than control mean pH value for females receiving 1000 mg/kg bw/day. The day 15 recovery data revealed values that were similar to treated or recovery control ranges, indicating recovery from the previous effects of treatment.

Effects in Organs
Organ weights
The organ weight changes consisted of higher mean liver weights for males receiving 1000 mg/kg bw/day when compared with control for animals killed after completion of 4 weeks treatment. In addition higher than control mean spleen weights were noted for females receiving 1000 mg/kg bw/day. The mean male liver weight and female spleen weight for animals previously treated at 1000 mg/kg bw/day were similar to control at the end of the 2 week recovery period, indicating recovery from the previous effects of treatment on organ weight.

Macroscopic findings
The macroscopic examination of animals killed at the end of the treatment period revealed a reduction in contents, mainly in the small intestine, of males receiving 1000 mg/kg bw/day. Hair loss was noted in both sexes receiving 1000 mg/kg bw/day. The macroscopic examination of the recovery animals did not reveal any changes that were considered to have been associated with previous treatment.

Histopathology
The microscopic examination of animals killed after completion of the 4 week treatment period and following a 2 week recovery period revealed slightly higher severity of extramedullary haemopoiesis in the spleen of main study male animals receiving 1000 mg/kg bw/day killed at the end of the treatment period.

Remarks – Results
Evidence of toxicity was seen at 1000 mg/kg bw/day. Higher than control values for white blood cell parameters among females were observed, although the cause of these changes is unknown as no microscopic changes were observed to indicate a target organ. The liver may be a possible target organ in the males as indicated by the higher than control liver weight and biochemical disturbances in alkaline phosphate, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglyceride and the plasma protein levels. No microscopic changes in the livers of these animals were observed. Water intake was high during the treatment period among both sexes, although urinary output was not affected and no microscopic changes were observed in the kidneys. By the end of the recovery period there was evidence of reversibility for most of the differences observed at the end of the treatment period.

Treatment-related findings were observed at 250 or 80 mg/kg bw/day. At 80 mg/kg bw/day lower than control urinary protein values in females, and transient pale faeces among both sexes was observed. These were not considered to be of toxicological importance. At 250 mg/kg bw/day a slight increase in weight gain was observed in females, together with disturbances in male alkaline phosphate values, female cholesterol values and urinary protein values. These changes were reversed by the end of the recovery period. The animals were in good general health and no microscopic changes were observed at this dose level. Therefore in the absence of any other treatment related findings 250 mg/kg bw/day is considered to be the No Observable Adverse Effect Level (NOAEL) in this study.

CONCLUSION
The No Observable Adverse Effect Level (NOAEL) was established as 250 mg/kg bw/day in this study, based on the lowest dose at which the changes observed were considered to be potentially adverse.

TEST FACILITY Test Facility B (2004b)

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.
Both plate incorporation procedure (Test 1) and pre-incubation procedure (Test 2) were used.

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2 uvrA (pKM101)
Metabolic Activation System	S9 fraction from Aroclor 1254-induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 5 - 5000 µg/plate. b) Without metabolic activation: 5 - 5000 µg/plate.
Vehicle	Suspension in water containing 0.15% bacteriological agar (Oxoid)
Remarks - Method	No significant protocol deviations. No separate preliminary study was performed, test 1 was used as the range-finding study.

RESULTS

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

* based on visible thinning of the background lawn.

Remarks - Results

No precipitation was observed. No visible thinning of the background lawn of non-revertant cells was observed, however a reduction in the revertant colony count was observed at 5000 µg/plate in some strains. This was particularly marked in strains TA1535 (test 2), TA1537 (both tests) and WP2 uvrA (both tests) in the presence of activation.

The test substance did not cause a marked increase in the number of revertants per plate of any of the tester strains either in the presence or absence of metabolic activation. The mean revertant colony counts for the solvent controls were within the 99% confidence limits of the current historical control range of the laboratory (except strains TA100 and CM891, where the mean counts in test 1 slightly exceeded the upper limits. This was not considered to affect the integrity of the study). Appropriate positive control chemicals (with S9 mix where required) induced substantial increases in revertant colony numbers with all strains, confirming sensitivity of the cultures and activity of the S9 mix.

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

TEST FACILITY Test Facility B (2002a)

7.9. Genotoxicity – in vitro mammalian chromosomal aberration test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.
Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 mix from Aroclor 1254-induced rat liver.
Vehicle	Culture medium, test substance added as suspension
Remarks - Method	No significant protocol deviations. Doses selected based on steep toxic response observed when tested up to 5000 μg/mL in a preliminary study.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	6.25, 12.5*, 25*, 50*, 75, 100,125	3 hours	20 hours
Test 2	3.13, 6.25*, 12.5*, 25*, 50, 75	3 hours	20 hours
Present			
Test 1	6.25, 12.5*, 25*, 50*, 75, 100,125	3 hours	20 hours
Test 2	6.25, 12.5*, 25*, 50*, 75	20 hours	20 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	≥78.13	>50	>50	negative
Test 2		>25	>25	negative
Present				
Test 1	≥78.13	>50	>50	negative
Test 2		≥50	>50	negative

* based on >50% reduction in mitotic index.

Remarks - Results	In both the absence and presence of S9 mix, the test substance caused no statistically significant increases in the proportion of metaphase figures containing chromosomal aberrations, at any dose level, when compared with the solvent control, in either test. No statistically significant increases in the proportion of polyploidy cells were seen in either test. Positive controls confirmed 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	Test Facility B (2004c)

7.10. Genotoxicity – in vitro mammalian cell gene mutation test

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.
Species/Strain	Mouse
Cell Type/Cell Line	Lymphoma/ L5178Y
Metabolic Activation System	S9 mix from Aroclor 1254-induced rat liver.
Vehicle	DMSO, test substance added as suspension
Remarks - Method	The protocol states that relative survival will be calculated in the evaluation of results, however exposure to T-71 was observed to cause

delayed toxicity after the exposure period. Relative survival does not take into account the cell loss after the exposure period and therefore where a statistically significant response to exposure of T-71 was seen, both relative survival and relative total growth was recorded.
This deviation from protocol is for information only and has no impact on the validity of the study.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0*, 20*, 30*, 32.5*, 35*, 37.5*, 40*, 42.5*, 45*, 47.5*, 50*	3	48	10-14 days
Test 2	0*, 10*, 20*, 30*, 32.5*, 35*, 37.5*, 40*, 45*, 50	24	48	10-14 days
Test 3	0*, 30*, 32.5*, 35*, 37.5*, 40*, 42.5*, 45*, 47.5, 50	24	48	10-14 days
Present				
Test 1	0*, 20*, 30*, 35*, 40*, 45*, 50*, 55, 60	3	48	10-14 days
Test 2	0*, 20*, 30*, 35*, 37.5*, 40*, 42.5*, 45*, 47.5*, 50*	3	48	10-14 days

*Cultures plated out for expression of the mutant phenotype.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test**	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	62.5	35	>50	Negative
Test 2		35	>50	Positive
Test 3		37.5	>50	Positive
Present				
Test 1	62.5	40	>60	Negative
Test 2		37.5	>50	Negative

*based on <50% relative survival or <50% relative suspension growth where a statistically significant increase in mutant frequency is seen.

Remarks - Results

In the second main test in the absence of S9 mix, a 24 hour exposure to 40 μg/ml of the notified chemical led to a 2.4 fold increase in mutant frequency above the negative control values. There was some evidence of a concentration dependant increase in mean mutant frequency. A third main test in the absence of S9 mix was carried out to assess whether this effect was reproducible. Statistically significant increases in mutant frequency representing 2.6, 2.4, and 6.2 fold increases above the negative control values were observed for exposure to 35, 37.5 and 40 μg/mL respectively. Throughout, in either the presence or absence of S9 mix, toxicity was observed after exposure.
In all tests the positive control substances increased mutant frequencies significantly.

CONCLUSION

The notified chemical was clastogenic to mouse lymphoma L5178Y cells treated in vitro for 24 hours in the absence of metabolic activation, under the conditions of the test.

TEST FACILITY

Test Facility B (2003c)

7.11. 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 CD-1
Route of Administration: Oral – gavage
Vehicle: 1% w/v methylcellulose
Remarks - Method: No significant protocol deviations. Since the preliminary toxicity test revealed no significant differences in toxicity between the sexes, the micronucleus test was preformed using males only.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
1-vehicle control	14 males	0	24 & 48
2	7 males	500	24
3	7 males	1000	24
4	14 males	2000	24 & 48
5 –positive control, M	5 males	12	24

M=mitomycin C.

RESULTS

Doses Producing Toxicity: The high dose (2000 mg/kg bw) reached the limit dose for a non-toxic test substance. There were no deaths or test substance-related clinical findings or remarkable bodyweight changes during the study. There was no statistically significant decrease in the PCE/NCE ratio, demonstrating that the test substance was not cytotoxic to the bone marrow.

Genotoxic Effects: The test substance is considered negative in this micronucleus assay. The test substance did not induce a statistically significant increase in the frequency of micronucleated PCE over the levels observed in the vehicle control. The frequency of micronucleated PCE in the positive control was significantly higher ($p<0.01$) than the vehicle control.

Remarks - Results: Although there is no evidence in this study that the chemical had reached the target tissue, based on other oral toxicity studies it is likely that the chemical reached the general circulation and hence the bone marrow.

CONCLUSION: The notified chemical was not clastogenic in this in vivo mouse micronucleus test under the conditions of the test.

TEST FACILITY: Test Facility B (2003d)

7.12. Genotoxicity – in vivo unscheduled DNA synthesis

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.
EC Directive 2000/32/EC B.39 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.

Species/Strain: Rat/Wistar HanIbm: WIST (SPF)
Route of Administration: Oral – gavage
Vehicle: 0.5% aqueous carboxymethylcellulose
Remarks - Method: No deviations from the protocol occurred that would affect the test's validity.
Male rats were used for the main test, as no sex-related differences were noted in a preliminary toxicity test.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
1a (vehicle control)	4 M	0	2
1b (vehicle control)	4 M	0	16
2a (low dose)	4 M	1000	2
2b (low dose)	4 M	1000	16
3a (high dose)	4 M	2000	2
3b (high dose)	4 M	2000	16
4a (positive control, DMH)	4 M	40	2
4b (positive control, 2-AAF)	4 M	100	16

DMH = N,N'-dimethylhydrazinedihydrochloride; 2-AAF = 2-acetylaminofluorene

RESULTS

Doses Producing Toxicity	Both doses of the notified chemical in the main study induced some toxic signs, such as reduction of spontaneous activity and ruffled fur. No deaths occurred.
Genotoxic Effects	The notified chemical did not, at any dose level, induce UDS in the hepatocytes of the treated animals as compared with concurrent controls and historical data.
Remarks - Results	Strong UDS responses were stimulated in the isolated hepatocytes of from animals treated with the positive controls, indicating that the test was functioning appropriately.

CONCLUSION The notified chemical did not induce DNA damage leading to increased repair synthesis under the conditions of this *in vivo* UDS test system.

TEST FACILITY Test Facility E (2004a)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE Notified chemical

METHOD

Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD, HPLC
Remarks - Method	No significant protocol deviations were reported.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	-1	7	66
14	-2	14	79
21	-1	21	81
28	-1	28	83

Remarks - Results The amount of the test substance relative to the charged amount determined directly by HPLC was 100% on the average in the three test substance degradation blocks and 102% in the stable block in water, resulting in a degradation rate of 3%, 3% and 1% (mean: 2%) in the three blocks. From these findings, the test substance T-71 was judged to be poorly degradable. The validation criteria for the test were satisfied.

CONCLUSION The notified chemical cannot be classed as ready biodegradable.

TEST FACILITY Test Facility F (2002)

8.1.2. Bioaccumulation

CONCLUSION Although the substance has a molecular weight that would not preclude absorption, the substance is not considered to have a high bioaccumulation potential based on the values of Log K_{oc} <1.25 and Log P_{ow} =2.5 and low fat solubility 0.025 mg/100 g Standard Fat, as reported in the physico-chemical tests conducted on the substance.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi-Static
EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-Static

Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	149 - 168 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Samples of the test substance weighing 200 mg were dispersed in separate 2.0 L flasks of test medium and ultrasonicated for one hour with intermittent vigorous shaking. These were then pooled to produce a stock dispersion of 100 mg/L. Serial dilutions of this stock dispersion were prepared with test medium to give the remaining nominal test concentrations. Analysis was performed on unfiltered solutions (as used for exposure) and additional samples were filtered using 0.45 µm cellulose nitrate filters prior to analysis to establish the quantities of test material in true solution. No significant protocol deviations were reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	None detected	7	0	0	0	0	0
2.2	2.1	7	0	0	0	0	0
4.6	4.4	7	0	0	0	0	0
10	9.3	7	0	0	0	0	0
22	21	7	0	0	0	0	0
46	45	7	2	7	7	7	7
100	94	7	7	7	7	7	7

LC50	30.7 mg/L at 96 hours (95% C.I. = 21-45 mg/L).
NOEC	21 mg/L at 96 hours.
Remarks – Results	There was only one marked reaction to exposure (other than death). After 2 and 4 hours exposure, remaining fish in 45 mg/L were observed to exhibit coughing. Differences between measured concentrations of filtered and unfiltered solutions suggest that the compound took some time to dissolve fully and that filtering did remove some of the test material, although there was no visual evidence of undissolved material and the solutions, whilst opaque, appeared homogenous in composition.

CONCLUSION The notified chemical is harmful to Rainbow trout.

TEST FACILITY Test Facility B (2004d)

8.2.2. Acute/chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

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

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Analytical Monitoring	HPLC
Remarks – Method	Samples of the test substance weighing 500 mg were dispersed in separate 5.0 L flasks of test medium and ultrasonicated for one hour with intermittent vigorous shaking. These were then pooled to produce a stock dispersion of 100 mg/L. Serial dilutions of this stock dispersion were prepared with test medium to give the remaining nominal test concentrations. Analysis was performed on unfiltered solutions (as used for exposure) and additional samples were filtered using 0.45 µm cellulose nitrate filters prior to analysis to establish the quantities of test material in true solution. No significant protocol deviations were reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	None detected	20	0	0
4.6	4.3	20	0	0
10	9.5	20	0	0
22	21	20	2	2
46	43	20	2	9
100	101	20	14	20

LC50	42 mg/L at 48 hours (95% C.I. = 35-52 mg/L).
NOEC	9.5 mg/L at 48 hours
Remarks – Results	Differences between measured concentrations of filtered and unfiltered solutions suggest that the compound took some time to dissolve fully and that filtering did remove some of the test material, although there was no visual evidence of undissolved material and the solutions, whilst opaque, appeared homogenous in composition. However, by the end of the 48 hour study period, values in both filtered and unfiltered samples were very similar. Based on these data, it is therefore considered appropriate to base the results on mean measured concentrations in unfiltered samples.

CONCLUSION The notified chemical is harmful to *Daphnia magna*.

TEST FACILITY Test Facility B (2003e)

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	Green alga *Selenastrum capricornutum*, Strain No CCAP 278/4
Exposure Period	72 hours
Concentration Range Nominal	0, 0.46, 1.0, 2.2, 4.6, 10 & 22 mg/L
Concentration Range Actual	0, 0.43, 0.99, 2.0, 4.0, 8.8 & 21 mg/L
Auxiliary Solvent	None
Analytical Monitoring	HPLC
Remarks – Method	Samples of the test substance weighing 200 mg were dispersed in separate 2.0 L flasks of test medium and ultrasonicated for one hour with intermittent vigorous shaking. These were then pooled to produce a stock dispersion of 100 mg/L. Serial dilutions of this stock dispersion were prepared with test medium to give the remaining nominal test concentrations. Analysis was performed on unfiltered solutions (as used for exposure) and additional samples were filtered using 0.45 µm cellulose nitrate filters prior to analysis to establish the quantities of test material in true solution. There were no deviations from the protocol that affected the outcome or validity of the study.

RESULTS

Biomass		*Growth*	
EbC50 mg/L at 72 h	*NOEC mg/L*	*ErC50 mg/L at 0-72 h*	*NOEC mg/L*
14 (95% C.I. = 12-16)	0.99	>21	0.99

Remarks – Results	All results are expressed in terms of the mean measured concentration of unfiltered samples. Unfiltered measured concentrations ranged from 86-98% of their nominal values at 0 hours and 85-101% of nominal at 72 hours. Comparison of the measured concentrations of the test substance in flasks with and without algae (at a nominal concentration of 10 mg/L) indicated that the presence of algal cells had not significantly affected the stability of the exposure solution at that concentration. All test and control cultures were inspected microscopically at 72 hours. No abnormalities were detected in any of the cultures examined. No cultures showed any signs of contamination by foreign algal cells or protozoa.
CONCLUSION	T-71 inhibited the growth of *Selenastrum capricornutum*, Strain No. CCAP 278/4 at concentrations tested in excess of 0.99 mg/L under the conditions of this test.
TEST FACILITY	Test Facility B (2003f)

8.2.4. 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 sludge from domestic sewage treatment plant mixed with synthetic sewage
Exposure Period	3 hours
Concentration Range Nominal	1- 1000 mg/L
Remarks – Method	No significant protocol deviations

RESULTS

IC50	>1000 mg/L

NOEC	1000 mg/L
Remarks – Results	Concentration-related inhibition of respiration rates was seen at and above nominal T-71 test concentrations of 30 mg/L. The highest tested concentration (1000 mg/L) in the definitive test caused 46% inhibition. Further testing at concentrations greater than 1000 mg/L was not considered to be appropriate because of the unrealistic test substance to sewage solids ratio for this test system. The three-hour EC20 of the test substance was estimated to be 64 mg/L. The three-hour EC50 values for 3,5-DCP were 20.0 mg/L (preliminary test) and 13.3 mg/L (definitive test), which fulfilled the validity criterion relating to sensitivity to inhibition (acceptable EC50 range 5 to 30 mg/L). The respiration rates between untreated controls (variation not greater than 15%) were also acceptable.
CONCLUSION	Concentration-related inhibition of respiration rates was seen at and above nominal T-71 test concentrations of 30 mg/L and the highest tested concentration (1000 mg/L) caused 46% inhibition. The EC20 of the test substance was estimated to be 64 mg/L, but the EC50 of the test substance could not be calculated and must be ≥ 1000 mg/L, the highest level tested.
TEST FACILITY	Test Facility B (2003g)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

With the exception of uncontained accidental spills, it is expected that release to the aquatic environment will not occur at any point in the notified chemical's life cycle. The majority will eventually be disposed of to landfill, where the notified chemical is expected to remain entrapped within an inert plastic matrix and will not be mobile. Over time, the notified chemical may very slowly undergo abiotic and biotic degradation. Some notified chemical may be disposed of by incineration, where by it is expected that it will be thermally decomposed to form various oxides of carbon, phosphorous and lithium.

9.1.2. Environment – effects assessment

The results of the ecotoxicity tests indicate that the notified chemical is harmful to aquatic organisms. The following Predicted No-Effect Concentration has been calculated using the lowest reported EC50 value.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga).	14.00	mg/L
Assessment Factor	100.00	
PNEC:	140.00	µg/L

9.1.3. Environment – risk characterisation

As release to the aquatic environment is not expected at any time during the life cycle of the notified chemical within Australia, a PEC/PNEC risk quotient can not be calculated.

The potential environmental exposure to the substance is considered to be negligible. Exposure to the environment from the formulation process involving the substance is of no concern, as formulation will be performed under controlled conditions in closed systems, and all the wastes generated will be disposed of by incineration at appropriate facilities. Stack gases are anticipated to be scrubbed, to remove oxides of carbon, phosphorus and lithium compounds in accordance with local regulations.

There will be the potential for only small environmental exposure from use of the end product and this will be widespread and disperse, as the notified chemical will be present at a concentration of <0.3% incorporated as a component of the plastic. Finished products made of the plastic containing the substance are anticipated to be disposed of by either incineration or landfill, as appropriate, at the end of their lifespan. It is considered unlikely that there will be any leaching or blooming of the substance from the plastic. In landfill the notified chemical will not be mobile and will slowly undergo abiotic and biotic degradation.

Therefore, based upon the proposed use and release patterns, the notified chemical is not expected to pose an unacceptable risk to the environment.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The notified chemical is imported as a powder. The particle size distribution indicates that all of the particles are inhalable (< 100 μm), with a significant proportion also being respirable (< 10 μm). The Coulter Counter experiment indicates that the proportion of respirable particles is approximately 25%, while the measurements taken during the acute inhalation study (using the Cascade Impaction method) indicate that the proportion is approximately 90%. This difference may arise due to the fact that the Coulter Counter method is not designed for water soluble compounds, and that the Coulter Counter method measures the particle size of the material as it is, while the Cascade Impaction method measures the particle size of the airborne dust of the material. The data from the Cascade Impaction method is therefore more relevant for determining the exposure during handling of the chemical.

Transport and warehousing workers will have low exposure, as under normal circumstances they will only handle sealed packages.

During formulation of plastic pellets the greatest potential for exposure (inhalation and dermal) to the notified chemical in powder form will occur during the weighing and mixing operations. Significant dermal and inhalation exposure to the powder may also occur during cleaning operations.

Exposure to the notified chemical powder will be minimised by the use of personal protective equipment such as safety glasses, protective clothing, gloves and a particle filter mask (during weighing and mixing) or a dust mask (during cleaning). Local exhaust ventilation is present in the weighing and loading areas, as well as at the mixers.

According to EASE (1997) modelling of this work environment, in which it is assumed that dry manipulation of non-fibrous, non-aggregating dust occurs in the presence of exhaust ventilation, the estimated atmospheric concentration during weighing and manual transfer is 2-5 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/h, 4 hour exposure and assuming that this was all either absorbed (respirable fraction) or ingested via the mucociliary clearance mechanism (inhalable fraction) systemic exposure after inhalation is estimated to be 0.15-0.37 mg/kg bw/day. This estimate assumes that no respiratory protection is worn.

Dermal exposure during manual weighing and addition of the notified polymer is estimated using EASE (1997) modelling, in which it is assumed that intermittent, non-dispersive use occurs with direct handling, to be in the range 0.1-1 $mg/cm^2/day$. Assuming 100% dermal absorption, a surface area of 980 cm^2 (half the total area of both hands and forearms, chosen due to the dusty nature of the powder), a bodyweight of 70 kg and that the chemical is present in the powder at 85%, this equates to a systemic exposure of 1.2-12 mg/kg bw/day. The model is a conservative one and may overestimate exposure. The model does not take into account the duration of the activity and the use of PPE and ventilation. Taking these factors into consideration the lower end of the modelled exposure range is considered to be a more appropriate estimate of the dermal exposure.

The total systemic exposure after both inhalation and dermal exposure is therefore estimated to be 1.4-12.4 mg/kg bw/day with the lower end of this range considered to be a more appropriate estimate when local exhaust ventilation is present and dermal protection (gloves and coveralls) is

worn.

Following formulation, exposure to the notified chemical is not expected as the notified chemical will be present at a concentration of < 0.3% and will be encapsulated in pellets. Workers handling the pellets at the formulation site and end-use site (injection moulding) are expected to wear gloves and eye-protection. Exhaust ventilation is present at the moulding machines.

9.2.2. Public health – exposure assessment

The exposure to the public will be negligible as the only contact anticipated is with articles in which the notified chemical is bound within the matrix and not bioavailable.

9.2.3. Human health – effects assessment

Acute toxicity
Based on tests in rats the notified chemical exhibits low acute toxicity via oral or dermal exposure, but is harmful via inhalation (LC50 = 3.11 mg/L/4 hours). The primary signs of toxicity in the acute inhalation study were effects on respiration, such as changes in the respiration rate, as well as noisy, laboured and gasping respiration. Ataxia was observed in all animals in the high dose group. Macroscopic abnormalities in the lungs were detected in all animals, including those that survived to necropsy.

Irritation and Sensitisation
The notified chemical was not irritating to skin when tested in a wetted powder form on rabbits. The notified chemical is slightly irritating to eyes, producing iridial inflammation (1/3 animals) and moderate conjunctival irritation (3/3 animals), which cleared by the 72-hour observation. No corneal injury was observed. There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation in a mouse local lymph node assay.

Repeat dose toxicity
In a 28-day repeat dose oral study in rats evidence of toxicity was observed at 1000 mg/kg bw/day including disturbances in white blood cell parameters among females, higher liver weights and biochemical disturbances in males, and higher water intake among both sexes. Treatment-related findings were observed at 80 and 250 mg/kg bw/day and thus a NOEL could not be established. However the changes observed at these lower doses were not considered adverse to the survival of the rat, and so a NOAEL of 250 mg/kg bw/day was established.

The effect of chronic inhalation exposure to the notified chemical was not studied. Based on the water solubility and molecular weight of the notified chemical, lung clearance should occur and over-loading of the lung is therefore not expected. However, based on the respiratory effects observed in the acute inhalation study, and the macroscopic abnormalities observed in the lungs of all animals (including the surviving animals and the low dose group) the possibility of chronic respiratory effects cannot be ruled out.

Genotoxicity
The notified chemical was not found to be mutagenic to *E. Coli* or *S. Typhimurium*. The notified chemical was clastogenic to mouse lymphoma cells treated *in vitro* for 24 hours in the absence of metabolic activation. However, the notified chemical did not cause mutation or chromosomal aberrations in human lymphocytes *in vitro*, mouse erythrocytes *in vivo*, or rat hepatocytes *in vivo*. The notified chemical is therefore not considered to be an *in vivo* mutagen or genotoxin.

Based on the acute toxicity effects after inhalation (LC50 = 3.11 mg/L/4 hours), the notified chemical is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

9.2.4. Occupational health and safety – risk characterisation

The risk of adverse effects is expected to be greatest for workers handling the powdered form of the notified chemical, i.e. formulation workers during weighing and mixing and cleaners. Once

formulation has occurred exposure to the notified chemical is not expected, and so the risk to workers during packaging and analysis of the formulated pellets at the formulation site, and during handling at the end-use site, is considered to be low.

Respiratory effects
Based on the available data the notified chemical is harmful by inhalation, with an LC50 value of 3.11 mg/L/4 h. The exposure conditions which would cause the equivalent toxic effects in humans (i.e. the LC50 value in humans) can be estimated from the formula below. As the primary toxic effects were respiratory and the majority of particles were respirable the surface area of the lungs was used as a normalising factor rather than body weight.

$$LC50(man) = LC50(rat) \times \frac{V_{min}\,(rat)}{V_{min}\,(man)} \times \frac{SA_{lung}\,(man)}{SA_{lung}\,(rat)} \times \frac{t_{exp}\,(rat)}{t_{exp}\,(man)} \times \frac{F_d\,(rat)}{F_d\,(man)}$$

$$= 3.11\ mg/L \times \frac{0.090\ L/min}{27\ L/min} \times \frac{54\ m^2}{0.34\ m^2} \times \frac{240\ min}{240\ min} \times \frac{0.04}{0.45}$$

$$= 0.146\ mg/L$$

$$= 146\ mg/m^3$$

Where : V_{min} = minute volume (value for rat from US EPA, 1994; value for human based on moderate activity level from EC TGD, 2003)
SA_{lung} = surface area of the lungs (Values from US EPA, 1994)
T_{exp} = exposure duration (animal exposure duration from acute inhalation study, human exposure duration from maximum time indicated by notifier)
F_d = deposition fraction (Values for nose-breathing rat and mouth-breathing human (worst-case) from Wolff and Dorato, 1997)

The chronic effects after repeated inhalation exposure to the notified chemical were not investigated, and therefore an inhalation NOAEL can not be determined. Based on the respiratory and lung effects seen in all animals in the acute inhalation study the notified chemical may pose a chronic respiratory hazard.

The notified chemical is imported in powder form, with the powder form being used only at the formulation site. The majority of the airborne dust during handling of this powder is expected to be of respirable size. EASE modelling of the powder handling at the formulation site (during weighing and mixing) estimates the exposure to be 2-5 mg/m^3 in the presence of local exhaust ventilation. This value is approximately 30-70 fold less than the estimated LC50 value in humans (146 mg/m^3). This LC50 value is a worst case estimate as it takes into account a worst case particle deposition scenario. Since an inhalation NOAEL could not be determined the safety of the EASE estimated atmospheric concentration after repeated exposure could not be established. The inhalation risk to workers handling the powder is therefore expected to be significant.

The notifier indicates that particle filter masks are expected to be worn by formulation workers during weighing and mixing, while cleaners are expected to wear dust masks. If the particle filter masks worn by formulation workers are capable of filtering out particles of respirable size, and are used and fitted correctly, the exposure to the airborne notified chemical, and therefore the risk to formulation workers, will be significantly reduced. However, unless the dust masks used by the cleaners are capable of filtering out particles of respirable size the risk to the cleaners will still be significant. Although currently imported as a powder, the risk to workers could be further reduced by the use of the notified chemical as granules or as a low-dust formulation.

Other systemic effects
The expected systemic exposure to the notified chemical after dermal contact and inhalation of the imported powder has been calculated using values from EASE modelling to be 1.4-12.4 mg/kg bw/day with the lower end of this range considered to be a more appropriate estimate

when local exhaust ventilation and protective gloves and clothing are in use. A dermal NOAEL was not determined, however a NOAEL of 250 mg/kg bw/day was established in a 28-day oral study in the rat. Assuming 100% absorption across the skin and 100% absorption/ingestion after inhalation, the comparison of this oral NOAEL with the estimated systemic exposure results in a margin of exposure (MOE) in the range 20-179. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, as the lower end of the estimated exposure is considered to be more appropriate, the risk of systemic effects (other than respiratory effects) to workers during the formulation process is considered acceptable when local exhaust ventilation is used and gloves and protective clothing are worn.

Local effects
The notified chemical is slightly irritating to the eye, however exposure is expected to be reduced by the use of safety glasses during all formulation processes. The risk of ocular effects is therefore considered to be low.

9.2.5. Public health – risk characterisation

The risk to public health is negligible as significant public exposure to the notified chemical is not anticipated.

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 and labelling details are:

Xn: Harmful
R20 Harmful by inhalation
S22: Do not breathe dust
S45: In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)
S51: Use only in well-ventilated areas

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***
Acute toxicity	4	Harmful if inhaled (dust)
Aquatic environment	Acute 3	Harmful to aquatic life
Aquatic environment	Chronic 3	Harmful to aquatic life with long lasting effects

10.2. Environmental risk assessment

Based upon the proposed use and release patterns, the notified chemical is not expected to pose an unacceptable risk to the environment.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is moderate concern to occupational health and safety under the conditions of the

occupational settings described for the workers handling the imported powder.

There is low concern to occupational health and safety under the conditions of the occupational settings described for the workers handling the formulated pellets and end-use articles.

10.3.2. Public health

There is negligible concern to public health when used in plastic products.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet- *Need revised MSDS*

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
Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:
  - Xn Harmful: R20 Harmful by inhalation

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥ 25%: Xn R20 Harmful by inhalation

- The following safety phrases should appear on the MSDS and label for the notified chemical:
  - S22: Do not breathe dust
  - S45: In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)
  - S51: Use only in well-ventilated areas

CONTROL MEASURES
Occupational Health and Safety

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

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Avoid generating and inhaling dusts
  - Clean-up operations should employ methods which avoid dust generation such as vacuuming (with appropriate filter) or wet clean-up
  - Where possible, utilise granulated or other low-dust formulations of the notified chemical
  - Avoid contact with eyes
  - Avoid contact with skin

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Full respiratory protection capable of filtering out respirable particles during processes where exposure to dust is likely
  - Safety eye protection
  - Protective clothing
  - Chemical-resistant gloves

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the 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.

Disposal

- The notified chemical should be disposed of by incineration or to landfill.

Emergency procedures

- In case of spill, dampen down powder and avoid dust. Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

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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