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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

CGP 2160

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, Water, Heritage and the Arts.

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:

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Ciba (Australia) Pty Ltd (ABN: 97 005 061 469)
235 Settlement Road
Thomastown VIC 3074

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Chemical Name; Other Names; CAS Number; Molecular Formula; Structural Formula; Molecular Weight; Purity; Identity and % Weight of Impurities and Additives/Adjuvants; Import Volume; Identity of Recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Hydrolysis as a Function of pH; Absorption / Desorption; Dissociation Constant; Acute Inhalation Toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
CEC/648

NOTIFICATION IN OTHER COUNTRIES
EU (ELINCS)
Canada (DSL) – (Limited Schedule I)
Japan (ENCS) – (Limited I)
USA (TSCA) – (2003)
China (IECSC) – (2003)
Korea (KECI) – (2001)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
CGP 2160

OTHER NAME(S)
Benzofuranone derivative
Lactone derivative
ODH 7800
TKA 40213
CGP 042

MOLECULAR WEIGHT
<500 Da

ANALYTICAL DATA
Reference NMR, IR, HPLC, ESI MS, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: white powder, no odour

Property	Value	Data Source/Justification
Melting Point/Freezing Point	111°C	Measured. Decomposed before boiling.
Boiling Point	Not observed under the test conditions	Measured.
Density	1067kg/m^3 at 20°C	MSDS
Vapour Pressure	8.07 x 10^{-13} kPa at 25 °C	Calculated
Water Solubility	< 0.1 mg/L at 20°C.	Measured. See below discussion.
Hydrolysis as a Function of pH	Not tested. Could not be conducted because of the very low water solubility.	Likely to be hydrolytically stable under ambient abiotic conditions in the environmental pH range of 4–9, based on its structure and very low water solubility.
Partition Coefficient (n-octanol/water)	log P_{ow} = 9.6 at 20°C	Measured. See discussion below.
Adsorption/Desorption	Not tested	Strongly hydrophobic and thus expected to sorb strongly to soils and organic matter.
Dissociation Constant	Not tested	Does not contain readily dissociable functionality.
Particle Size	Inhalable fraction (<100 μm): ~99.9% Respirable fraction (<10 μm): 64.78% MMAD* = 7.274 μm	Measured
Flash Point	Not determined	Low vapour pressure solid
Solid Flammability	Not highly flammable	Measured
Autoignition Temperature	Not observed to autoignite	Measured up to 450 °C
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	Measured

* MMAD = Mass Median Aerodynamic Diameter

DISCUSSION OF PROPERTIES

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

Water Solubility

Analytical data from aquatic toxicity testing confirm the very low water solubility.

Partition Coefficient (n-octanol/water)

The high partition coefficient is consistent with the structure of the notified chemical, and its solubility in organic solvents (acetonitrile and ethyl acetate).

Reactivity

The notified chemical was found to be not highly flammable and not to auto ignite up to 450 °C or to be explosive or oxidising. The notified chemical is incompatible with strong acids, strong bases and strong oxidising agents. Static discharges should also be avoided. The decomposition temperature has been determined to be ~260°C and typical decomposition products include oxides of carbon and other toxic gases/vapours (not identified).

5. INTRODUCTION AND USE INFORMATION

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

The notified chemical will be imported at concentrations of >95% in powder form.

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

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

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
Ciba (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported by sea in 40-kg fibreboard boxes, and transported by road to the notifier's warehouse and stored until distributed to customers for production of masterbatches and thence to plastic processors. The finished thermoplastic polymer products containing the notified chemical will be distributed to numerous premises around Australia.

USE
Antioxidant stabiliser for thermoplastic polymers. It may be used in automotive applications such as bumper bars, interior trim, marine fittings and industrial applications such as building panels, roofing, construction, housing and crates.

OPERATION DESCRIPTION
Masterbatch production
The notified chemical (> 95% concentration) will be emptied into a feed hopper of the blending vessel under local exhaust ventilation and blended with other ingredients in a closed vessel to concentration levels of up to 15% in the resulting powder blend. It will then likely be further processed into masterbatches, involving weighing of the powder containing the notified chemical and loading into mixers under local exhaust ventilation. The resulting masterbatch is expected to contain the notified chemical at concentrations of less than 0.1%.

Moulding of plastic articles
The masterbatches will then be transported to customer sites where they may be mixed with other ingredients (notified chemical present at less than 0.1%) and subsequently moulded into the shapes of the required plastic articles.

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 (days/year)*
Transport drivers	1 - 3	60 mins per trip	4 – 6
Warehouse operators	1 – 5	30 mins per load/unload	4 - 10
Plant operators – Masterbatch production	1 – 4	10 – 20 mins/day	< 50
Plant operators – Plastic moulding	> 100	4hr/day	> 50
Laboratory technicians	1 – 4	10 – 20 mins/day	< 50

EXPOSURE DETAILS
Dermal, ocular and inhalation exposure may occur during emptying/weighing, blend discharge and quality control operations during powder blending and masterbatch production involving the notified chemical (concentrations up to > 95%).

Masterbatch production
Inhalation exposure to the solid form of the notified chemical may be significant, given that its particle size is

largely in the inhalable range, with a significant proportion also in the respirable range. The expected enclosed nature of the mixing vessels, and the local exhaust ventilation in place during handling operations should lower the potential for dermal, ocular and inhalation exposure. EASE modelling of similar processes indicates up to a 25-fold reduction in the predicted inhalation dust exposure during processes where local exhaust ventilation is present (estimated to be 2-5 mg/m^3), compared to those where it is absent (estimated to be 5-50 mg/m^3). Assuming an inhalation rate of 2.5 m^3/hr (US EPA 1997), moderate/medium level activity, and workers weighing an average of 70 kg, these dust exposures are equivalent to 0.28-0.7 mg/kg bw/day (LEV present) and 0.7 - 7 mg/kg bw/day (LEV absent).

EASE modelling of the initial manual emptying of the notified chemical into the feed hopper during powder blending was performed to estimate dermal exposure of workers to the notified chemical. The following assumptions were used in determining these estimates: direct handling (no control measures in place), non-dispersive use (only used by workers with a knowledge of the processes), and intermittent contact level (assumed to be 2-10 events per day). The predicted dermal exposure to the notified chemical is 0.1-1 mg/cm^2/day, which is equivalent to 2.3-23 mg/kg bw/day, based on the assumptions outlined by the European Commission (EC 2003). Note that if it is assumed that effective local exhaust ventilation is in place (ie. not direct handling), then the dermal exposure is predicted by EASE modelling to be 'very low'.

Plastic moulding
Once incorporated into the masterbatch the notified chemical would be encapsulated in the polymer matrix, therefore exposure during plastic moulding is expected to be very low.

6.1.2. Public exposure
Members of the public are expected to come into contact with a diverse range of plastic products containing the notified chemical, however, it will be incorporated into the polymer matrix and thus exposure is expected to be negligible.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	low toxicity LD50 >2000 mg/kg bw
Rat, acute dermal toxicity	low toxicity LD50 >2000 mg/kg bw
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic
Developmental and reproductive effects (one generation study)	NOAEL 1000 mg/kg bw/day

Toxicokinetics
No information is available on the toxicokinetics of the notified chemical. However, absorption of the notified chemical from the gastrointestinal tract or dermally is expected to be limited by its low water solubility and high lipophilicity. However, gastrointestinal tract absorption may occur by micellular solubilisation.

There is potential for inhalation of the notified chemical, given the significant proportion that is of inhalable (>99%) and respirable size (~65%). Its small particle size, low water solubility and high log P value indicate that it is likely to be absorbed across the respiratory tract epithelium and accumulated. Clearance of inhaled material from the upper respiratory tract is also expected to lead to some ingestion (European Commission, 2003).

Toxicological end points
The notified chemical was found to be slightly irritating to the eyes (some iridial and conjunctival irritation observed in all animals). It was of low toxicity for all other tested end points. It was non-irritating and non-

sensitising to the skin, as well as being non-genotoxic. In addition, the notified chemical was of low acute oral and dermal toxicity, and upon repeated oral exposure no effects were observed that were considered to be adverse, both during a 28 day test, and in a test to determine developmental/reproductive effects.

No data was submitted on the inhalation toxicity of the notified chemical. Irritant or toxic effects as a result of inhalation of the notified chemical cannot be ruled out.

Health hazard classification
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 highest exposure of workers to the notified chemical (concentrations up to > 95%) may occur during emptying/weighing, blend discharge and quality control operations (dermal, ocular and inhalation) for powder blending and masterbatch production. Inhalation exposure can also lead to ingestion.

A NOAEL of 1000 mg/kg bw/day (the highest dose tested) for the notified chemical was established in a 28 day oral study in rats. This NOAEL has been used below as an indication of the effects by other routes (dermal and inhalation) in calculating the risk of repeated exposure.

Using a worst case scenario with no LEV in place and worker exposure for 4 hours per day, EASE modelling of inhalation exposure (7 mg/kg bw/day) and dermal exposure (23 mg/kg bw/day) results in a margin of exposure (MOE) of 33 by combining the exposures via the two routes. With LEV in place, inhalation exposure is estimated to be 0.7 mg/kg bw/day, and dermal exposure to be very low. This results in an increase in the MOE to 1430, which is considered to be an acceptable level (as it is > 100). The risk will be further reduced due to the fact that the notified chemical will not always be present at 100% in the powders that are handled, exposure times are expected to be < 1 hour per day, and PPE is expected to be worn.

Worker exposure is not likely to occur during the later stages of processing or in handling moulded articles containing the notified chemical, as it will be incorporated in the polymer matrix and will not be bioavailable.

Given the available test data on the notified chemical and the implementation of appropriate control measures to minimise exposure, the notified chemical is not considered to pose an unacceptable risk to workers.

6.3.2. Public health
As the public are only expected to come into contact with the notified chemical when it is incorporated into a polymer matrix and not bioavailable, the risk to public health is not considered to be unacceptable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported for blending into powder blends (levels up to 15%) for further processing into masterbatches (levels < 0.1%). Environmental release of the notified chemical is unlikely to occur following accidental spillage of imported containers containing the notified chemical during importation (shipping), handling, storage or local transportation due to established controls in place.

The typical formulation of a powder blend and masterbatch will take place in a highly automated operation allowing for minimal release. During production of these blends, measured quantities of the notified chemical are mixed with other components in a blending vessel, where they are homogeneously mixed. The mix is then compacted, granulated and packed into bags.

All dust and other residuals (e.g. in the bags) are removed using vacuum systems and recycled into subsequent batches of the blended products. As a consequence of these automated systems, it is anticipated that there will

be no release during production of the powder blends. It is expected that similar systems in place at those plants producing masterbatches will lead to minimal release of the notified chemical.

Empty import bags will most likely be disposed to landfill. However, due to the use of vacuum systems during production, any residual of the notified chemical left in these bags is expected to be insignificant.

The production methods used in all stages of production of the polymer articles into which the notified chemical will be incorporated mean that almost all the notified chemical will be firmly encapsulated in polymer matrices with little likelihood for release from plastic articles.

RELEASE OF CHEMICAL FROM USE
Since the notified chemical will be firmly incorporated in a polymer matrix, its eventual fate will be associated with that of the polymer articles. It is likely that this will comprise a diverse group of products, but it may be assumed that since these are plastic they will be eventually disposed to landfill, or possibly be incinerated.

In landfill there is little possibility of significant leaching of the notified chemical, since it will be firmly incorporated into the polymer matrix. However, the polymer articles will be very slowly degraded through the agency of various biological and abiotic processes operative in landfill structures, and it could be expected that the notified chemical will also be destroyed by these processes. In this case, it will be degraded to water, methane and carbon oxides. Incineration of articles containing the notified chemical will result in its immediate combustion, with formation of water vapour and oxides of carbon.

RELEASE OF CHEMICAL FROM DISPOSAL
Residues of the notified chemical in emptied imported boxes will not be rinsed but will be collected by waste management contractors for disposal, incineration or recycling. No wastewaters containing the notified chemical are generated during manufacture of masterbatches or blended products. Products containing the notified chemical will have widespread and diffuse use pattern in Australia and waste finished products will be mostly sent to landfill for disposal.

7.1.2 Environmental fate

The majority of the imported quantity of the notified chemical will be disposed of to landfill, with most of this irreversibly combined with articles. In landfill, the notified chemical is expected to be immobile, and to undergo very slow degradation. Minimal aquatic exposure is expected.

Environmental fate studies indicate that the notified chemical is not readily biodegradable, and has a low potential for bioconcentration in fish. For the details of the environmental fate studies please refer to Appendix C. Although the high octanol/water partition coefficient suggests a potential for bioconcentration in fish, aquatic exposure to the notified chemical is expected to remain low when it is used as proposed in the production of plastic articles. The test finding of slight bioconcentration is consistent with the structure of the notified chemical, which would be expected to metabolise in and depurate rapidly from fish.

7.1.3 Predicted Environmental Concentration (PEC)

No PEC has been calculated as no significant releases of the notified chemical to the aquatic compartment are expected to occur. Analytical data from aquatic toxicity testing indicate that the notified chemical is strongly hydrophobic and unlikely to exceed an aquatic concentration of 0.001 mg/L even if released to the aquatic environment.

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 WAF	Nontoxic to fish up to the limit of water solubility.
Daphnia Toxicity	EC50 > 100 mg/L WAF	Nontoxic to daphnids up to the limit of water solubility.
Algal Toxicity	EC50 > 100 mg/L WAF	Nontoxic to green algae up to the limit of water solubility.

The results from aquatic toxicity testing indicate that the notified chemical is nontoxic to fish, daphnids and green algae at concentrations up to its solubility limit. Tests were conducted on filtered, water accommodated fractions (WAF) prepared at a single loading rate of 100 mg/L.

7.2.1 Predicted No-Effect Concentration

It is neither meaningful nor necessary to calculate an environmental risk quotient as the notified chemical is not expected to be released into aquatic ecosystems in ecotoxicologically significant amounts. The notified chemical is not harmful to aquatic life at concentrations up to the solubility limit.

7.3. Environmental risk assessment

The notified chemical is unlikely to be released into aquatic ecosystems in environmentally significant concentrations, based on the intended use pattern, the potential for removal from waster water streams by physical processes (especially adsorption to solids), and the absence of effects in aquatic toxicity testing. Therefore, the risk of an adverse effect on the environment from the intended use of the notified chemical is acceptably low.

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)].

and

As a comparison only, the notified chemical was not classified as Hazardous using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations, 2003). This system is not mandated in Australia and carries no legal status but is presented for information purposes.

Human health risk assessment

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

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

Environmental risk assessment

On the basis of the proposed use pattern and the low potential for environmental exposure, the notified chemical is not considered to pose a risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Local exhaust ventilation during operations for powder blending and masterbatch production.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid inhalation of powder.

- Employers should ensure that the following personal protective equipment is used by workers during powder blending and masterbatch production to minimise occupational exposure to the notified chemical:
  - Respiratory protection where powder is present.
  - Gloves and eye protection.

  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 *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 containment, collection and subsequent safe disposal.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
  - information becomes available as to the inhalation effects of the notified chemical;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from use in thermoplastic polymers for automotive applications, marine fittings and industrial applications, or is likely to change significantly;

- the amount of chemical being introduced has increased from 1 tonne per annum, or is likely to increase, significantly;
- 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.

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/Freezing Point 111ºC

Method EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Exothermal decomposition was observed to commence at 260 ºC.
Test Facility Bayer (1999a)

Boiling Point Boiling was not observed when heated up to a temperature of 375 ºC

Method EC Directive 92/69/EEC A.2 Boiling Temperature.
Test Facility Bayer (1999b)

Vapour Pressure 8.07×10^{-13} kPa

Method Program SRC-Log Kow, version 1.57 estimate for Microsoft Windows, Copyright (C) William Meylan, 1994.

Water Solubility < 0.0001 g/L at 20ºC

Method EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Column Elution Method (HPLC). The very low water solubility of the test substance is confirmed by the analytical results for the water accommodated fractions used for aquatic toxicity testing (C.2.1., C.2.2 and C.2.3). Final measured concentrations in these tests did not exceed the limit of quantification (0.000001 g/L). The highest initial measured test concentration was 0.000029 g/L.
Test Facility Bayer (1999c)

Partition Coefficient (n-octanol/water) log P_{ow} = 9.6 at 20ºC

Method EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks HPLC Method. The column was calibrated with six reference substances. The substance with the longest retention time was triphenylamine (log P_{ow} = 5.7). As there was no established calibration standard with log P_{ow} > 9.6, the log P_{ow} of the test substance was determined by linear extrapolation.
Test Facility Bayer (1999d)

Particle Size

Method Laser diffraction particle size analysis

Range (μm)	*Mass (%)*
< 1.263	10
< 7.042	50
< 22.341	90

Remarks Inhalable fraction (<100 μm): ~99.9%
Respirable fraction (<10 μm): 64.78%
MMAD* = 7.274 μm
Test Facility Chilworth (2008)

Flammability Not highly flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Test Facility Bayer (1999e)

Autoignition Temperature Not observed under the conditions of the test

Method EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Test Facility Bayer (1999e)

Explosive Properties Not explosive

Method EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks Tested for thermal stability, mechanical sensitivity (drop weight test and friction mill).
Test Facility Bayer (1999e)

Oxidizing Properties Not oxidising

Method EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Test Facility Bayer (1999e)

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/Wistar
Vehicle	Propylene glycol
Remarks - Method	No significant protocol deviations.
RESULTS	
LD50	>2000 mg/kg bw
Remarks - Results	No mortality, significant clinical signs, or abnormal macroscopic findings were observed at the dose level of 2000 mg/kg bw.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	NOTOX (1999a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/Wistar
Vehicle	Propylene glycol
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations.
RESULTS	
LD50	>2000 mg/kg bw
Remarks - Results	No mortality or abnormal macroscopic findings were observed at the dose level of 2000 mg/kg bw. Red staining was observed in some animals on day 2 (recovery between days 3 – 7). Scales were observed on the treated skin area of one animal between days 3 – 7.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	NOTOX (1999b)

B.3. 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 (male)
Vehicle	Moistened with water
Observation Period	72 hours
Type of Dressing	Semi-occlusive

Remarks - Method No significant protocol deviations.

RESULTS

Remarks - Results No skin irritation was observed

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

TEST FACILITY NOTOX (1999c)

B.4. 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 (male)
Observation Period 72 hours
Remarks - Method No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.7	0.3	1	2	< 72 hr	0
Conjunctiva: chemosis	0	0	0.3	2	< 48 hr	0
Conjunctiva: discharge	0	0	0.3	1	< 48 hr	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	1	< 24 hr	0

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

Remarks - Results Slight dulling of the normal lustre and epithelial damage (10% of the total corneal area) was observed in one animal 24 hours after treatment (resolved within 72 hours).
Iridial irritation was observed in all animals and had resolved within 24 hours after instillation. Irritation of the conjunctivae (redness, chemosis and discharge) was observed in all animals and had completely resolved within 48 hours in two animals and within 72 hours in the third animal.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY NOTOX (1999d)

B.5. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation - Guinea Pig Maximisation Test
EC Directive 96/54/EC B.6 Skin Sensitisation - Guinea Pig Maximisation Test
Species/Strain Guinea pig/Himalayan albino
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 2%
topical: 50%
MAIN STUDY
Number of Animals Test Group: 10 Control Group: 5

INDUCTION PHASE	Induction Concentration: intradermal: 2% topical: 50%
Signs of Irritation	Following intradermal injections with 2% test substance, 3/10 animals displayed slight or well-defined erythema. Following intradermal injection of 4% test substance with Freunds' Complete Adjuvant (FCA), well-defined to severe erythema or necrosis were observed, and in the corresponding control animals, slight to moderate erythema were observed. Moderate erythema was observed in all animals, including the control group, following intradermal injection with FCA and water alone. Following epidermal application, some animals displayed scabbing, with one animal showing slight erythema and another animal showing severe erythema. Observations in the corresponding control groups were similar. Such reactions were considered to have been enhanced by treatment with SDS.
CHALLENGE PHASE	
1st challenge	topical: 50%
Remarks - Method	10% sodium dodecyl sulfate (SDS) was applied to the injection sites 24 hours prior to topical induction. The vehicle used for dilution of test substance was corn oil.

RESULTS

Remarks - Results	None of the animals were observed to have been sensitised.

CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	NOTOX (1999e)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/Wistar Crl: (WI) BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Propylene glycol
Remarks - Method	No significant protocol deviations.

RESULTS

Dose mg/kg bw/day	*Number and Sex of Animals*	*Mortality*
control	5 males, 5 females	0
50	5 males, 5 females	0
150	5 males, 5 females	1
1000	5 males, 5 females	0

Mortality and Time to Death

One female treated with 50 mg/kg/day died following blood sampling on the day of scheduled necropsy. This was considered to be incidental.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

In 3/5 females receiving 150 mg/kg/day, increased levels of urea (statistically significant, with large standard deviation) and some increases in creatinine (not statistically significant) were observed, which may be indicative of possible effects in the kidneys of these animals. However, no changes were observed in the kidney weights or at macroscopic examination in these animals. Given that the effects were not dose related the changes were considered not to be induced by treatment.

Remarks – Results

There were no toxicologically relevant changes in any of the following parameters following treatment with the notified chemical: clinical signs, functional observations, body weights, organ weights, food consumption, clinical laboratory investigations (haematology and clinical biochemistry), macroscopic and microscopic examination.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study.

TEST FACILITY NOTOX (1999f)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from rat liver induced with Aroclor 1254
Concentration Range in Main Test	a) With metabolic activation: 10 - 1000 µg/plate b) Without metabolic activation: 10 - 1000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. The doses used in the main test were based on the results of a preliminary range finding test.

RESULTS

Remarks - Results	The test material caused no visible reduction in the growth of the bacterial background lawn and no significant increase in the frequency of revertant colonies at any dose level in any strain. Precipitation was observed at and above 1000 µg/plate in all tested strains at the start and end of incubation. The results of the positive and negative controls confirmed the sensitivity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	NOTOX (1999g)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese hamster
Cell Type/Cell Line	V79 cells
Metabolic Activation System	S9 mix from rat liver induced with Phenobarbital and β-naphthoflavone
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	31.25, 63*, 125*, 250*, 500, 1000, 2000	4 hr	20 hr
Test 2	7.5*, 15*, 30*, 75, 150, 300	20 hr	20 hr
Present			
Test 1	2.5, 5, 7.5, 15, 20*, 30*, 60*	4 hr	20 hr
Test 2	10, 18, 22*, 25, 28*, 35, 50*	4 hr	20 hr

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 125	~ 125	> 2000	Equivocal*
Test 2	-	> 15	> 300	Negative
Present				
Test 1	> 15.6	> 20	> 60	Negative
Test 2	-	> 28	> 50	Negative

Remarks - Results

*In Test 1 without metabolic activation, the number of aberrant cells following treatment with 63 µg/mL test substance was slightly above the historical control data range of the negative control. At the other concentrations used in this test, aberration rates were within the control range and there were no dose related increases observed.

There were no biologically relevant increases in the frequencies of polyploid cells following treatment with the test substance. The test concentrations used in the main test were relatively low due to the toxicity of the test substance. The results of the positive and negative controls confirmed the sensitivity of the test system.

CONCLUSION

The notified chemical was not clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test.

TEST FACILITY

BSL (2006)

B.9. 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: NMRI BR mice (SPF)
Route of Administration: Intraperitoneal injection
Vehicle: Corn oil
Remarks - Method: No significant protocol deviations.

Dose mg/kg bw	*Number and Sex of Animals*	*Sacrifice Time hours*
Corn oil*	5M	24
Corn oil*	5M	48
1000*	5M	24
1000*	5M	48
Cyclophosphamide	5M	48

* Dosed twice with a 24 hour interval to reach the limit dose of 2000 mg/kg bw.

RESULTS

Doses Producing Toxicity	No signs of test substance-related clinical findings. The ratio of the polychromatic to normochromatic erythrocytes (PCE/NCE) was similar to that of the control animals.
Genotoxic Effects	There were no increases in the frequency of micronucleated polychromatic erythrocytes of the bone marrow of animals treated with the test substance. While it could not be substantiated that the chemical reached the bone marrow (through a change in the PCE/NCE ratio) the study authors attributed this to a lack of toxicity of the test substance.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo mouse micronucleus test.
TEST FACILITY	NOTOX (2000)

B.10. Toxicity to reproduction – one generation study

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 415 One Generation Reproduction Toxicity Study. EC Directive 87/302/EEC B.34 One Generation Reproduction Toxicity Test.
Species/Strain	Wistar rats Crl: (WI) BR
Route of Administration	Oral – gavage
Exposure Information	Exposure period - female: 57-63 days Exposure period - male: 99 or 100 days
Vehicle	Propylene glycol
Remarks – Method	Several deviations from the standard protocol were noted, however, these were not considered to have adversely affected the outcome of the study.

RESULTS

Dose mg/kg bw/day	*Number and Sex of Animals*	*Mortality*
0	24 M, 24 F	0
50	24 M, 24 F	1
150	24 M, 24 F	1
1000	24 M, 24 F	0

Mortality and Time to Death

Two females died before the completion of the study, with one (treated with 50 mg/kg/day) sacrificed due to prolapse of the uterus on day 1 of lactation, and the other (treated with 150 mg/kg/day) found dead on day 6. This animal showed hunched posture, piloerection and laboured breathing on day 4 and 5 of treatment. These deaths were considered to be incidental and not related to treatment.

Effects on Parental (P) animals:

There were no clinical signs, body or organ weight changes, food consumption changes, macroscopic or microscopic findings that were considered to be related to treatment.

A total of ten males and seven females were suspected of infertility, however, such findings were considered normal in rats of this age and strain. In one male rat that had been treated with the highest dose, marked seminiferous atrophy (bilateral) was observed in the testes and marked oligospermia (bilateral) was observed in the epididymides. This may have caused the infertility of this animal.

Percentage mating and gestation indices were unchanged in the treatment groups. The fertility index and conception rate for rats treated with the highest dose was lower (83.3%) compared to that for the lower dose

levels and controls (95.7-95.8%). The study authors noted that this was within the limits of the historical control data range (79.2% to 100%).

Overall, the parental animals were considered to be unaffected by treatment.

Effects on 1st Filial Generation (F1)

One pup in the low dose group displayed effects in the left eye, including scabs and dessication, on days 21 and 22 of lactation. One pup of the high dose group showed an enlarged head on day 21 of lactation, which was found to be due to hydrocephalis. At this low incidence, these macroscopic findings were considered to be unrelated to treatment.

The following observations were made in some pups: small appearance, constricted liver and spleen, autolysis, hemia diaphragmatica of the liver, cannibalism, wounds, scabs, cold, no milk, chromodacryorrhoea, pale appearance, missing tail apex, and alopecia. Alopecia, when observed, was mainly found in several pups of the same litter. These effects were not considered to be related to treatment.

In general, development of pups was considered to be unaffected by treatment with the test substance.

CONCLUSION

The parental, reproduction, breeding and developmental No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study. This is consistent with the results of the 28 day oral repeat dose study in rats.

TEST FACILITY NOTOX (2007)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Combined and cultivated sludge from ten different places in Japan.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	HPLC
Remarks - Method	The biodegradability of the test substance (0%) was monitored by measuring oxygen consumption. The test was validated by measuring the biodegradability of a reference substance (aniline at 100 mg/L), for which biodegradability reached 78%.
RESULTS	The notified chemical is not readily biodegradable.
TEST FACILITY	Institute of Ecotoxicology Co., Ltd (2005a)

C.1.2. Bioaccumulation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 305 Bioconcentration: Flow-through Fish Test.
Species	
Exposure Period	Exposure: 28 days Depuration: not measured
Auxiliary Solvent	Tween 20 was used, at five times the concentration of the test substance.
Concentration Range	Nominal: 0.05 and 0.5 mg/L
Analytical Monitoring	HPLC. The raw data were not provided.
Remarks - Method	It is not possible to provide detailed comments on the test method as only the summary report was provided. The test substance was continuously introduced under flow-through conditions. Concentrations of the test substance in fish and water were determined by HPLC. Tween 20 was used to assist dispersion, because of the very poor water solubility of the notified chemical. Although the high octanol/water partition coefficient suggests a potential for bioconcentration, the test finding of slight bioconcentration is consistent with the structure of the notified chemical, which would be expected to metabolise in and depurate rapidly from fish. Bioconcentration factors reached their maximum values after 21 days.
RESULTS	
Bioconcentration Factor	Maximum 44 at 0.5 mg/L and < 30 at 0.05 mg/L (mean of two fish).
CT50	Not measured because of low bioconcentration factor.
Remarks - Results	No visible abnormalities were seen in the fish.
CONCLUSION	The notified chemical is slightly concentrating in fish.
TEST FACILITY	Institute of Ecotoxicology Co., Ltd (2005b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – flow-through.
Species	Zebra fish (*Danio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	228.6 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Four replicates of 7 fish were used as controls, and the same number for the limit test (water accommodated fraction at 100 mg/L, prepared by filtration after stirring a supersaturated stock dispersion). Test vessels were conditioned with the test solution for 1 hour, with renewal of the test solution before introduction of the fish, and continuous renewal through the test by introducing the stock solution under flow-through conditions. Initial and final measured test concentrations (0.0008 and 0.0004 mg/L) were below the limit of quantification (0.001 mg/L), while the initial measured concentration of the stock solution was 0.0208 mg/L.
RESULTS	No mortalities were observed. Results are expressed as loading rates.
LC50	> 100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	Note that the summary provided for the bioconcentration test (C.1.2) reports an LC50 in this species of 87 mg/L. Use of a dispersing agent such as Tween 20 is assumed.
CONCLUSION	The notified chemical is nontoxic to fish up to the limit of water solubility.
TEST FACILITY	ECT Oekotoxikologie GmbH (2006a)

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.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	255 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	Four replicates of 5 daphnids were used as controls, and the same number for the limit test (water accommodated fraction at 100 mg/L, prepared as for the fish test). Test vessels were conditioned before introduction of the daphnids, as for the fish test, but there was no renewal of the test medium during the 48 hour exposure period. Initial and final measured test concentrations were 0.029 and 0.001 mg/L respectively, while the initial measured concentration of the stock solution was 0.0235 mg/L.
RESULTS	No immobilised daphnids were observed. Results are expressed as loading rates.
LC50	> 100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours

CONCLUSION	The notified chemical is nontoxic to daphnids up to the limit of water solubility.
TEST FACILITY	ECT Oekotoxikologie GmbH (2006b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Limit test – water accommodated fraction at loading rate of 100 mg/L, prepared as for the fish and daphnid tests. Test vessels were preconditioned as in the fish and daphnid tests. Test media were not renewed during the 72 hour exposure period.
Auxiliary Solvent	None
Water Hardness	14.7 mg $CaCl_2.2H_2O$/L
Analytical Monitoring	HPLC
Remarks - Method	Initial and final measured test concentrations were 0.0014 and 0.0005 mg/L respectively, while the initial measured concentration of the stock solution was 0.0011 mg/L. The sensitivity of the algal culture tested was verified against the reference substance potassium dichromate. The cell concentration in the control cultures increased during the test by a factor of 191.2, satisfying the validity criterion of 16.
RESULTS	No significant growth inhibition was seen in exposed cultures compared with controls. Differences in growth rate and biomass production at 72 hours were less than 1%.
CONCLUSION	The notified chemical is nontoxic to green algae up to the limit of water solubility.
TEST FACILITY	ECT Oekotoxikologie GmbH (2006c)

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