File No: STD/1462

May 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

XP-7866

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

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This 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

TABLE OF CONTENTS

SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1462	Albemarle Singapore Pte Ltd	XP-7866	No	≤ 100 tonnes per annum	Flame retardant in plastics

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following isolation and engineering controls to minimise occupational exposure to the notified chemical, as introduced in the neat form:
  - Local exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced in the neat form:
  - Avoid contact with eyes
  - Avoid generation of dusts

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced in the neat form:
  - Goggles
  - Dust masks where exposure to dusts may occur

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

- A copy of the (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental releases of the notified chemical should be handled by physical containment, collection and subsequently 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:

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a flame retardant in plastics, or is likely to change significantly;
- the amount of chemical being introduced has increased from 100 tonnes per annum, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
Albemarle Singapore Pte Ltd (ABN: 30 061 231 229)
490 Lorong 6
Toa Payoh #09-10
HDB Hub, Biz 3

Singapore 310490

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, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities, use details, and import volume.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
USA
Korea (2012)
Canada (2012)

2. IDENTITY OF CHEMICAL

MARKETING NAME
XP-7866

MOLECULAR WEIGHT
< 500 Da

ANALYTICAL DATA
Reference NMR, IR, UV data were provided.

3. COMPOSITION

DEGREE OF PURITY > 99%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Point	295 °C	Measured
Boiling Point	> 450 °C at 101.3 kPa	Measured
Density	1440 kg/m^3 at 20.5 °C	Measured
Vapour Pressure	5.4 x 10^{-13} kPa at 25 °C	Measured
Water Solubility	3.26 × 10^{-4} g/L at 20°C	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ = 53.5 days (pH 4, 25°C) $t_{1/2}$ = 25.4 hours (pH 7, 25°C) $t_{1/2}$ = 0.418 hours (pH 9, 25°C)	Measured
Partition Coefficient (n-octanol/water)	log P_{OW} = 2.36 at 40°C	Measured
Adsorption/Desorption	log K_{OC} = 3.49 at 40°C	Measured
Dissociation Constant	Not determined	Not expected to dissociate under environmental conditions (pH 4-9) due to absence of dissociable functional groups
Particle Size	Inhalable fraction (< 100 μm): 28.6% Respirable fraction (< 10 μm): 8.15%	Measured

Flash Point	Not determined	Not determined – fire retardant
Flammability	Not highly flammable	Measured
Autoignition Temperature	> 295 °C	Measured
Explosive Properties	Negative	Based on structure
Oxidising Properties	Negative	Based on structure

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as the neat chemical and as a component of resin preparations. The notified chemical will not be manufactured in Australia.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 50	< 50	50-100	50-100	50-100

PORT OF ENTRY
Sydney or Melbourne

TRANSPORTATION AND PACKAGING
The notified chemical will be supplied to the manufacturer of resin masterbatches in supersacks or drums (30 or 55 gallon with plastic liner or insert). The notified chemical will not be repackaged or reformulated in Australia.

USE
Flame retardant in plastics

OPERATION DESCRIPTION
At the plastic processing site, the notified chemical will be manually transferred from the import containers to the additive hopper, and will be metered into an extruder with the resin and other additives to produce prepeg or masterbatch pellets, which will be further cured/moulded into finished articles. Once cured/moulded, the finished articles will contain the notified chemical at up to 5% concentration.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

EXPOSURE DETAILS
Dermal and possibly accidental ocular exposure to the neat notified chemical (purity > 99%) may occur during transfer of the notified chemical from the import container into the additive hopper. Although the notified chemical has a low vapour pressure (5.4×10^{-13} kPa at 25 °C), there is also potential for inhalation exposure when handling the neat notified chemical as introduced in the powdered form as it contains a percentage of particles in the inhalable and respirable range. Once added to the extruder, exposure to the notified chemical is not expected.

Workers will be exposed to finished plastic material incorporating the notified chemical at < 5% concentration.

However, once incorporated into finished plastic products, the notified chemical will be chemically incorporated into a resin matrix and will not be bioavailable.

6.1.2. Public Exposure

The notified chemical is intended for industrial use only, and will not be available to the public. Direct exposure would therefore not be expected.

The public may be exposed to finished plastic products containing the notified chemical at < 5% concentration. However, once incorporated into finished plastic products, the notified chemical will be chemically incorporated into a resin matrix and will not be bioavailable.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose (oral gavage) toxicity – 28 days.	NOAEL 1000 mg/kg bw/day (systemic toxicity) NOEL 1000 mg/kg bw/day (neurotoxicity)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro Mammalian Chromosome Aberration Test	non genotoxic

Toxicokinetics, metabolism and distribution.

The notified chemical was shown to hydrolyse under aqueous conditions, but the hydrolysis was more pronounced at high pH (estimated half-life of 0.418 hours at pH 9) compared to low pH (estimated half-life of 53.5 days at pH 4), which although indicating that the notified chemical will undergo hydrolysis under physiological conditions, it is likely that hydrolysis will be minimal in the gastrointestinal tract.

Due to the low molecular weight (< 500 Da), the notified chemical may be absorbed across the gastrointestinal tract. Dermal absorption, however, is expected to be limited by the low water solubility.

Acute toxicity.

Based on studies conducted in rats, the notified chemical is of low acute oral and dermal toxicity.

Irritation and sensitisation.

The notified chemical is non-irritating to the skin, but is mildly irritating to the eye of rabbits. There was no evidence that the notified chemical is a skin sensitiser in mice.

Repeated Dose Toxicity.

In a 28-day oral gavage repeated dose toxicity study in rats the NOAEL was determined to be 1000 mg/kg bw/day. With respect to treatment-related neuropathological changes, the NOEL was determined to be 1000 mg/kg bw/day in the same study.

Mutagenicity/Genotoxicity.

The notified chemical was non mutagenic in a bacterial reverse mutation test. There was no evidence of clastogenicity in an *in vitro* mammalian chromosome aberration test in cultured human lymphocytes. Based on these studies, the notified chemical is not expected to be genotoxic.

Health hazard classification

Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on available studies, the notified chemical is of low hazard with only the potential for presenting as a slight eye irritant. As introduced in the neat powdered form there is the potential for inhalation exposure. The acute inhalation toxicity of the notified chemical is not known. However, the notified chemical is of low acute oral and dermal toxicity, and has a NOAEL of 1000 mg/kg bw/day; therefore inhalation toxicity is not expected.

Workers at risk of eye irritation effects and inhalation exposure will be those handling the neat notified chemical as introduced in the powdered form. Therefore, provided control measures are in place to minimise worker exposure when handling the neat notified chemical as introduced, including the use of local exhaust ventilation and PPE (in particular protective goggles and dust masks where appropriate), the risk to workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

The general public is not expected to be exposed to the notified chemical; hence the risk to public health under the proposed use is not considered unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is to be imported into Australia as a component of resin preparations and as the neat chemical. Accidental spills during transport or resin manufacture are expected to be collected with inert material and disposed of to landfill. Cleaning of equipment will result in the notified chemical being chemically incorporated into a resin matrix, which will be used in further preparations or disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical is to be chemically incorporated into a resin matrix, where the notified chemical will no longer exist in its original form. Therefore, no release of the notified chemical is expected during the use phase.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical will share the fate of the article into which it is chemically incorporated. At the end of their useful life, these articles are expected to be disposed of to landfill. The notified chemical is not expected to be available in end products and therefore no release is anticipated. Approximately 0.3% of the notified chemical production volume is expected to remain in shipping containers. This is likely to share the fate of the shipping containers and be disposed of to landfill.

7.1.2. Environmental Fate

The majority of the notified chemical is expected to be chemically incorporated into resin matrices and no longer exist in the original form. Therefore, notified chemical incorporated into plastic articles is not expected to leach or be bioavailable, and no significant release is expected based on the reported use pattern. A small proportion of the notified chemical may be released to landfill via the disposal of shipping containers. Notified chemical disposed of to landfill is not expected to experience a high degree of mobility, based on the low water solubility and high log K_{OC} of the notified chemical. Therefore, leaching of the notified chemical from landfill to surface waters is expected to be limited.

The notified chemical is not readily biodegradable. However, based on the log K_{OW}, the notified chemical is not expected to bioaccumulate, and is expected to readily hydrolyse under environmental conditions (pH 4-9). Ultimately, the notified chemical is expected to degrade via biotic and abiotic processes in soil and surface waters to form water, oxides of carbon, and inorganic salts.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated as significant release of the notified chemical to the aquatic compartment is not expected based on the reported use pattern.

7.2. Environmental Effects Assessment

Ecotoxicity data for the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C. No toxic effects were observed at the concentrations used in these studies, which appear to represent the functional limit of solubility in the environment. Therefore, the notified chemical is not expected to be harmful to aquatic life at the limit of solubility.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity (96 h)	LC50 > 153 µg/L	Not expected to be harmful to fish
Daphnia Toxicity (48 h)	LC50 > 79 µg/L	Not expected to be harmful to aquatic invertebrates
Algal Toxicity (96 h)	EC50 > 26 µg/L	Not expected to be harmful to algae
Inhibition of Bacterial Respiration (3 h)	EC50 > 1000 mg/L	Not inhibitory to bacterial respiration

Study reports identified difficulty in achieving the reported water solubility. Additionally, as the notified chemical experiences rapid hydrolysis, constant concentrations of the notified chemical were not maintained throughout these studies; especially for the algal study, where static conditions were used. Nevertheless, as no toxic effects were observed at the concentrations obtained, and the concentrations used appear to represent the functional limit of solubility in the environment, it is concluded that the notified chemical is not expected to be harmful to aquatic life at the limit of solubility. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification of Chemicals (GHS; United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

Calculation of the predicted no-effect concentration (PNEC) was not considered necessary as no significant release of the notified chemical to the aquatic compartment is expected from the reported use pattern.

7.3. Environmental Risk Assessment

The Risk Quotient (PEC/PNEC) was not calculated as limited release of the notified chemical to the aquatic compartment is expected based on the reported use pattern. The majority of the imported notified chemical will be chemically incorporated into resin matrices and is not expected to leach or be bioavailable. Therefore, on the basis of limited aquatic exposure and the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 295 ± 0.5 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Differential scanning calorimetry
Test Facility Harlan (2011a)

Boiling Point > 450 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Remarks Differential scanning calorimetry Boiling was not observed below 450 °C.
Test Facility Harlan (2011a)

Density 1.44×10^3 kg/m^3 at 20.5 ± 0.5 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Pycnometer method
Test Facility Harlan (2011b)

Vapour Pressure 5.4×10^{-13} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks Vapour pressure balance
Test Facility Harlan (2011a)

Water Solubility 3.26×10^{-4} g/L at 20°C

Method OECD TG 105 Water Solubility.
Remarks Column Elution Method
Test Facility Wildlife International (2011a)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$*
4	25	53.5 days
7	25	25.4 hours
9	25	0.418 hours

Remarks Tier 2 testing conducted as hydrolysis of the test item was greater than 10% over 5 days. Study conducted using HPLC analysis.
Test Facility Harlan (2011c)

Partition Coefficient (n-octanol/water) log P_{OW} = 2.36 at 40°C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method
Test Facility Wildlife International (2011b)

Adsorption/Desorption log K_{OC} = 3.49 at 40°C

Method OECD TG 121 Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks
Test Facility Harlan (2011c)

Particle Size

Method (Designed to be compatible with) OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (μm)	*Mass (%)*
< 100	28.6
< 10.0	8.15
< 5.5	0.916

Test Facility Harlan (2011b)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks None
Test Facility Harlan (2011d)

Autoignition Temperature > 295 °C

Method EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks No autoignition below the melting temperature.
Test Facility Harlan (2011d)

Explosive Properties Not predicted to be explosive

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Based on structure
Test Facility Harlan (2011d)

Oxidizing Properties Not predicted to be oxidising

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks Based on structure
Test Facility Harlan (2011d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Wistar (RccHan™:WIST)
- Vehicle: Distilled water
- Remarks - Method: No significant protocol deviations.

A sighting test was initially performed with one test animal at a dose level of 2000 mg/kg. Subsequently, four additional test animals were dosed at 2000 mg/kg.

Clinical observations were made at 0.5, 1, 3, and 4 hours after dosing and subsequently once daily for fourteen days.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1F	2000	0
2	4F	2000	0

- LD50: > 2000 mg/kg bw
- Signs of Toxicity: No signs of systemic toxicity were noted.
- Effects in Organs: No abnormalities were noted at necropsy.
- Remarks - Results: No mortalities occurred and there were no signs of either systemic toxicity observed during clinical observations or abnormalities noted at necropsy. All animals showed expected gains in bodyweight over the observation period.

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

TEST FACILITY: Harlan (2011e)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Wistar (RccHan™:WIST)
- Vehicle: Distilled water
- Type of dressing: Semi-occlusive.
- Remarks - Method: No significant protocol deviations.

A single dose of the notified chemical (2000 mg/kg) was applied to the intact skin of ten test animals (five females and five males) for 24 hours using a semi-occluded dressing.

Clinical observations were made at 0.5, 1, 3, and 4 hours after dosing and subsequently once daily for fourteen days.

RESULTS

- LD50: > 2000 mg/kg bw
- Signs of Toxicity - Local: No signs of local toxicity were noted.
- Signs of Toxicity - Systemic: No signs of systemic toxicity were noted.
- Effects in Organs: No abnormalities were noted at necropsy.

Remarks - Results	There were no mortalities and all test animals showed expected gains in bodyweight.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Harlan (2011f)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Males
Vehicle	Water
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	The notified chemical moistened sufficiently with water to give a paste was first applied using a semi-occluded patch to the intact skin of one test animal at three sites on the dorsal/flank area. The patches were removed at time points of 3 minutes, 1 hour, and 4 hours. The notified chemical was then applied to the intact skin of two additional test animals under a semi-occluded patch for a 4-hour exposure period. Observations were recorded after 1, 24, 48, and 72 hours after removal of the patches. During the experiment involving a 3 minute exposure, observations after one hour were not recorded.

RESULTS

Remarks - Results	No irritation or corrosion effects were observed in the animals during the test period. No mortalities were reported and the test animals showed expected gain in bodyweight during the study.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Harlan (2011g)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Males
Observation Period	72 hour
Remarks - Method	No protocol deviations were reported. A single animal was used initially, followed by two further animals.

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	0.7	0.7	2 (1 h)	< 72 h	0
Conjunctiva: chemosis	0.3	0.3	0.3	1	< 48 h	0
Conjunctiva: discharge	0	0	0	1 (1 h)	< 24 h	0
Corneal opacity	0	0	0	-	-	0
Iridial inflammation	0	0	0	-	-	0

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

Remarks - Results	The single application of the notified chemical to the non-irrigated eye of three rabbits produced moderate conjunctival irritation after one hour, minimal conjunctival irritation after 24 and 48 hours, and all eyes appeared normal at the 72 hour observation. The body weights of the animals during the study remained normal.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Harlan (2011h)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca Strain, female
Vehicle	Dimethyl formamide
Remarks - Method	A preliminary screening test was carried out on a single mouse to determine a suitable concentration range to be used during the main test that would not produce systemic toxicity or excessive local irritation. No concurrent positive control group was added to the study. A reduced local lymph node assay, using ten animals (five animals for each of the test and the control vehicle) was conducted by the Test Facility using the same methods, animal strain and supplier with α-hexylcinnamaldehyde in dimethyl formamide as the positive control. No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	947.72	-
10	846.82	0.89
25	1400.12	1.48
50	856.61	0.90

Remarks - Results	White residual test item was observed on the ears of animals treated with concentration of the notified chemical at 25% and 50% from Day 2 and Day 1, respectively. There were no deaths reported. There were no signs of systemic toxicity noted in the test or control animals during the test. Bodyweight changes of the test animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Harlan (2011i)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents

Species/Strain	Rat/Wistar (Han™:RccHan™:WIST)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Distilled water
Remarks - Method	A 28 Day study was performed on 100 test animals: 60 test animals were used in the main study, while an additional study for neuropathological evaluation was performed using 40 test animals. In both studies test animals were administered the notified chemical at dose levels of 0, 30, 300, and 1000 mg/kg bw/day. The dose levels were chosen based on the results of a previous toxicity study (Project Number 41101788) undertaken by the same test facility. The latter study was not included in the dossier. Clinical observations were made during the week immediately prior to dosing, and subsequently 30 minutes, one hour and five hours post dosing. On weekends the five hour observation post dosing was not performed. During the treatment free period the test animals were observed daily. The animals were observed for signs of functional/behavioural toxicity, and the sensory reactivity of the test animals to stimuli, were carried out on Day 1 and weekly thereafter. The observations were carried out approximately two hours after dosing. The tests were carried out weekly during the treatment-free period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M/5F	0	0/10
low dose	5M/5F	30	0/10
mid dose	5M/5F	300	0/10
high dose	5M/5F	1000	0/10
control recovery	5M/5F	0	0/10
high dose recovery	5M/5F	1000	0/10

Mortality and Time to Death

There were no unscheduled deaths during the study.

Clinical Observations

There were no clinical observations detected for treated or control animals throughout the treatment or recovery periods of the study.

There were no treatment-related changes observed during behavioural assessments (weekly open-field observations), functional performance tests, or sensory reactivity assessments.

There were no adverse effects on body weight changes, food or water consumption during the study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no toxicologically significant haematological effects or changes in urinalytical parameters for animals treated with the test substance.

Effects in Organs

There were no toxicologically significant effects on organ weights and there were no macroscopic findings suggestive of abnormalities resulting from the test substance.

Centrilobular hepatocyte hypertrophy of minimal severity was noted in the livers of five (3 males and 2 females) high dose animals; however no such effects were noted in the recovery group. In the absence of enzymatic changes the study authors consider the minor lesions in the liver to represent an adaptive response to the test item.

Microvesicular vacuolation in the corticomedullary junction tubules of the kidneys was noted in four of the high-dose males; however this effect was not noted in the females or in the recovery group. In the absence of any degenerative or inflammatory changes, the study authors did not consider this finding to represent an adverse effect.
Minor lymphoid depletion in the spleen was noted in two high dose males but was not evident in the recovery group. In the absence of any organ weight changes, the minor stress-induced response was considered by the study authors to be unrelated to test substance toxicity.
Diffuse hypertrophy of the cortical zona fasciculate in the adrenal glands was reported in several animals in the mid- and high-dose groups. The findings were minimal/slight and not evident in the recovery group. In the absence of any correlating organ weight changes, these findings were considered by the study authors not to represent an adverse effect of treatment.
No lesion that indicated a neurotoxic effect was observed and there was no impact on spermiogenesis.

Remarks – Results
Treatment related effects were observed in animals dosed at 1000 and 300 mg/kg bw/day. The findings mainly consisted of histopathological changes in the liver, spleen, kidneys and adrenal glands but were not considered as adverse effects.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on the lack of adverse health effects for systemic toxicity at this dose.
The No Observed Effect Level (NOEL) was established as 30 mg/kg bw/day in this study, based on the lack of treatment-related effects for systemic toxicity at this dose.
The No Observed Effect Level (NOEL) for neurotoxicity was established as 1000 mg/kg bw/day in this study, based on the lack of treatment-related neuropathological changes at this dose.

TEST FACILITY Harlan (2012)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test
Plate incorporation procedure/Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Rat S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 50 to 5000 µg/plate b) Without metabolic activation: 50 to 5000 µg/plate
Vehicle	Dimethyl formamide
Remarks - Method	The direct plate incorporation method was used during the range-finding test (Test 1). During the replicate assay the exposure condition was changed from plate incorporation to pre-incubation (Test 2). During all tests, at concentrations of 5000 µg/plate, manual counts were performed due to excessive test item precipitation.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5,000			
Test 1		> 5,000	≥ 5,000	negative
Test 2		> 5,000	≥ 5,000	negative
Present	> 5,000			
Test 1		> 5,000	≥ 5,000	negative
Test 2		> 5,000	≥ 5,000	negative

Remarks - Results Precipitation was observed at 5,000 µg/plate in all experiments. Slight

toxicity was observed in the absence of metabolic activation at a dose of 5000 µg/plate.

The test material was tested up to the maximum recommended dose level of 5000 µg/plate. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose level either with or without metabolic activation or exposure.

All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

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

TEST FACILITY Harlan (2011j)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test

Species/Strain	Human
Cell Type/Cell Line	Peripheral lymphocytes
Metabolic Activation System	Rat S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks - Method	A range-finding study was conducted in the presence and absence of metabolic activation at concentrations between 8.96 µg/mL to 2294 µg/mL, with a 4 hour exposure time followed by a 20 hour recovery period. A similar range-finding study was conducted in the absence of metabolic activation and with a continuous exposure period of 24 hours. The concentration of induced rat liver homogenate metabolising system (S9) used in Test 1 and Test 2 were 2% and 1% of the final concentration, respectively. Due to formulation practicalities, the maximum dose was limited to 2294 µg/mL.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	17.92, 35.84, 71.69*, 143.38*, 286.75, 573.5*, 1147, 2294*	4	24
Test 2	17.92, 35.84, 71.69, 143.38, 286.75*, 573.5*, 1147*, 2294*	4	24
Present			
Test 1	17.92, 35.84*, 71.69, 143.38*, 286.75, 573.5*, 1147, 2294*	4	24
Test 2	17.92, 35.84, 71.69, 143.38, 286.75*, 573.5*, 1147*, 2294*	4	24

*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	> 2294	> 2294	≥ 143.38	negative
Test 2	> 2294	> 2294	≥ 17.92	negative
Present				

Test 1	> 2294	> 2294	≥ 17.92	negative
Test 2		> 2294	≥ 71.69	negative

Remarks - Results	Evidence of toxicity was observed in all three groups, but no clear dose-related effects were observed. The positive and vehicle controls gave satisfactory responses, confirming the validity of the test system. The test material did not induce any statistically significant increases in the frequency of cells with aberrations, or in the numbers of polyploid cells.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Harlan (2011k)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	Filter paper treated with notified chemical used as test substance
Analytical Monitoring	Not reported
Remarks - Method	The method was conducted in accordance with good laboratory practice (GLP). The test was conducted using concentration of 5 mg/L due to the inhibition of microorganisms by test substance at a concentration of 10 mg/L.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
14	0	14	72
28	0	28	87

Remarks - Results	Relevant test validity criteria were met. The toxicity control attained 39% degradation, confirming that the test substance (at 5 mg/L) was not inhibitory to microorganisms used in the test.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Harlan (2011l)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-Static.
Species	*Pimephales promelas*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	132 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	The method was conducted in accordance with good laboratory practice (GLP). Media renewal occurred at approximately 24 hours and 72 hours.

RESULTS

Concentration µg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control		2 × 10	0	0	0	0	0
20	11	2 × 10	0	0	0	0	0
40	23	2 × 10	0	0	1	0	0
80	34	2 × 10	0	0	0	0	0
160	75	2 × 10	0	0	0	0	0
320	153	2 × 10	0	0	0	0	0

LC50	> 153 µg/L at 96 hours.
NOEC	153 µg/L at 96 hours.
Remarks – Results	Relevant test validity criteria were met. An additional fish was accidently killed from the 40 µg/L treatment group at 48 hours but was excluded from the mortality count. No toxic effects were observed. The results of this study are presented based on the mean measured concentration of the test substance in the test solutions.
CONCLUSION	The notified chemical is not expected to be harmful to fish.
TEST FACILITY	Wildlife International (2012c)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Semi-Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	172 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	The method was conducted in accordance with good laboratory guidelines (GLP). Media renewal occurred at 48 hours.

RESULTS

Concentration µg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control		2 × 10	0	0
20	6.5	2 × 10	0	0
40	15	2 × 10	0	0
80	19	2 × 10	0	0
160	36	2 × 10	0	0
320	79	2 × 10	0	0

LC50	> 79 µg/L at 48 hours
NOEC	79 µg/L at 48 hours
Remarks - Results	Relevant test validity criteria were met. A number of *Daphnia* were observed to have been trapped at the water surface but appeared normal after gentle submersion. The results of this study are presented based on the mean measured concentration of the test substance in the test solutions.
CONCLUSION	The notified chemical is not expected to be harmful to aquatic invertebrates.
TEST FACILITY	Wildlife International (2012d)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test - Static.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours
Concentration Range	Nominal: 20, 40, 80, 160, 320 µg/L Actual: 5, 11, 15, 16, 26 µg/L
Auxiliary Solvent	None
Water Hardness	Not reported

Analytical Monitoring	HPLC
Remarks - Method	The method was conducted in accordance with good laboratory guidelines (GLP).

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
µg/L at 96 h	*µg/L at 96 h*	*µg/L at 96 h*	*µg/L at 96 h*
> 26	26	> 26	26

Remarks - Results	Relevant test validity criteria were met. The results of this study are presented based on the mean measured concentration of the test substance in the test solutions.

CONCLUSION The notified chemical is not expected to be harmful to algae.

TEST FACILITY Wildlife International (2011e)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated sewage
Exposure Period	3 hours
Concentration Range	Nominal: 10, 100, 1000 mg/L
Remarks – Method	The method was conducted in accordance with good laboratory guidelines (GLP).

RESULTS

EC50	> 1000 mg/L
NOEC	1000 mg/L
Remarks – Results	Relevant test validity criteria were met.

CONCLUSION The notified chemical does not inhibit microbial activity.

TEST FACILITY Harlan (2011m)

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