File No: EX/171 (STD/1376)

April 2012

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
(NICNAS)

FULL PUBLIC REPORT

Substituted Isothiazolone in Bioban 518S and Bioban 551S

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

TABLE OF CONTENTS

FULL PUBLIC REPORT

This assessment report is for an extension of original assessment certificate for Substituted Isothiazolone in Bioban 518S. Based on the submission of new information by the extension notifier, some sections of the original assessment report for Dow Chemical Australia Ltd have been modified. These modifications have been made under the heading *'Extension Application'* in the respective sections.

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT	CHEMICAL OR TRADE NAME	HAZARDOUS SUBSTANCE	INTRODUCTION VOLUME	USE
EX/171 (STD/1376)	Rohm and Haas Australia Pty Ltd	Substituted Isothiazolone in Bioban 518S and Bioban 551S	Yes	< 40 tonnes per annum	A preservative for water based coatings at < 0.1% concentration

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the data provided, the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)], with the following risk phrases:

R25 Toxic if swallowed
R21 Harmful in contact with skin
R34 Causes burns
R43 May cause sensitisation by skin contact

and

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below.

	Hazard category	*Hazard statement*
Acute toxicity	3	Toxic if swallowed (oral)
Acute toxicity	4	Harmful in contact with skin (dermal)
Corrosive	1	Causes severe skin burns and eye damage
Skin sensitiser	1	May cause an allergic skin reaction
Aquatic environment	Acute Category 1	Very toxic to aquatic life
	Chronic Category 1	Very toxic to aquatic life with long lasting effects

Human health risk assessment
Under the conditions of the occupational settings described (with engineering controls and personal protective equipment for reformulation workers), 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 PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose an unacceptable risk to the environment.

Risk assessment relating to extension applicant
The use and environmental fate described in the extension application are not expected to impact the outcomes of the original human health and environment risk assessment and recommendations.

Recommendations
REGULATORY CONTROLS
Hazard Classification and Labelling

- Safe Work Australia, should consider the following health hazard classification for the notified chemical:
  - T; R25 Toxic if swallowed
  - Xn; R21 Harmful in contact with skin
  - C; R34 Causes burns
  - Xi; R43 May cause sensitisation by skin contact

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥ 25%: R25, R21, R34, R43
  - 10% ≤ conc < 25%: R22, R43, R34
  - 5% ≤ conc < 10%: R36/37/38, R43, R22
  - 3% ≤ conc < 5%: R43, R22
  - 1% ≤ conc < 3%: R43

- The notified chemical should be classified under the Australian Dangerous Goods Code (NTC, 2007) considering its toxicity and effects on the environment.

Health Surveillance

- The notified chemical should be considered by the Safe Work Australia for development of health surveillance guidelines.

- As the notified chemical is a potential skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin allergies.

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical (at concentrations < 10%):
  - Local exhaust ventilation during reformulation of coatings
  - Automated processes when possible

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced and during reformulation of coatings (< 10% concentration):
  - Prevent leaks and spills
  - Avoid contact with skin and eyes
  - Do not inhale vapour

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced and during reformulation of coatings:

- Chemical resistant gloves
- Safety glasses or face mask
- Coveralls

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

- Spray applications should be carried out in accordance with the Safe Work Australia *National Guidance Material for Spray Painting* [NOHSC (1999)] or relevant State and Territory Codes of Practice.

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

Secondary Notification

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

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

(1) Under Section 64(1) of the Act; if
- the notified chemical is imported in solid form;
- the notified chemical is imported at concentrations ≥ 10%;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a preservative of water-based paints at < 0.1% concentration, or is likely to change significantly;
- the amount of chemical being introduced has increased from 40 tonnes/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 MSDS of a product containing 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.

Extension Application
The extension applicant has provided an MSDS of a product containing the notified chemical which was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the extension applicant.

Substituted Isothiazolone in Bioban 518S and Bioban 551S

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Holder of the original Assessment certificate (STD/1376)
Dow Chemical Australia Ltd (ABN 72 000 264 979)
541-583 Kororoit Creek Road
Altona VIC 3018

Applicant for an Extension of the Original Assessment Certificate:
Rohm and Haas Australia Pty Ltd (ABN 29 004 513188)
4th Floor, 969 Burke Road
Camberwell, VIC 3124

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, other names, molecular and structural formula, molecular weight, analytical data, degree of purity, use details, import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant, particle size, flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

OTHER NAME(S)
Substituted isothiazolone

MARKETING NAME(S)
Bioban 518S (Product containing < 10% notified chemical)
Bioban 551S (Product containing < 10% notified chemical)

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

3. Composition

DEGREE OF PURITY > 98%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight) None

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Pale yellow crystalline solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	53.3°C	Measured
Boiling Point	324.6°C at 101.3 kPa	Measured
Density	1452.7 kg/m^3 at 20°C	Measured
Vapour Pressure	4.249 x 10^{-5} kPa at 25°C 2.342 x 10^{-5} kPa at 20°C	Measured
Water Solubility	14.6 to 16.0 g/L at 20.1°C, pH = 3.5 to 7.8	Measured
Hydrolysis as a Function of pH	$t_{½} \geq 1$ year at 25°C	Measured
Partition Coefficient (n-octanol/water)	log K_{OW} = 1.4 at 20°C	Measured
Surface Tension	60.8 mN/m at 19.8°C	Measured
Adsorption/Desorption	log K_{OC} = 2.0 to 2.3 at 20°C	Measured
Dissociation Constant	pKa ~ -2	Measured
Particle Size	Not determined	The notified chemical will only be imported in aqueous solution
Flammability	Not highly flammable	Measured
Autoignition Temperature	> 400°C	Measured
Explosive Properties	Unlikely to possess explosive properties	Measured and estimated
Oxidising Properties	Unlikely to possess oxidising properties	Estimated

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

Reactivity
The notified chemical is stable under normal conditions of use. Tests on the thermal stability and packaging stability of the notified chemical were performed, indicating that it remained stable and did not adversely affect its packaging under the test conditions.

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However the data above do not address all Dangerous Goods endpoints. Therefore consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as an aqueous solution at a concentration of < 10%.

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

Original Certificate Holder

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 10	< 10	< 10	< 15	< 20

Extension Application

Year	*1*	*2*	*3*	*4*	*5*

Tonnes	< 10	< 10	< 10	< 15	< 20

Total

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 20	< 20	< 20	< 30	< 40

PORT OF ENTRY
Melbourne, Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Dow Chemical, Melbourne

TRANSPORTATION AND PACKAGING
The notified chemical will be imported by ship in poly containers (~20kg), drums (~200L) and intermediate bulk containers (~1000L). It will then be transported by road or rail from the port to the notifier's warehouse or directly to reformulators.

Following reformulation, the coating products containing the notified chemical will be packaged, stored and transported in 1L, 4 L, 10L and 20L steel cans and pails to end use sites.

USE
The notified chemical will be used as a preservative for water-based coatings at < 0.1% concentration. Such coatings may be used for wood, furniture, automotive applications, etc. Approximately 80% of the import volume of the notified chemical will be used for industrial applications, with the remaining 20% used by tradesmen and do-it-yourself (DIY) users.

OPERATION DESCRIPTION
Coating formulation
Transfer of the notified chemical (< 10% concentration) to a blending vessel (typically a 10,000L stainless steel vessel) may occur by workers opening the pails and drums containing the notified chemical, manually weighing the required quantities and manually charging the vessel. Alternatively, the notified chemical (< 10% concentration) may be metered directly from the storage drums/containers into the blending vessel using semi-automated processes. Following the addition of other ingredients (pigments and resin), the mixture will be pumped into a separate vessel where the remaining ingredients (additives and resin) will be added and mixed to give the final product containing the notified chemical at < 0.1%. Samples of the final product will be taken for quality control purposes. The final product will be transferred into smaller containers by gravity from the bottom of the mixing vessel through a filter and filling lines.

Coating application
Coating products containing the notified chemical at < 0.1% concentration will be applied to substrates using spray (75%), brush (20%) or roller (5%). Prior to application, the paint will be manually stirred and poured into trays or into the spray guns. Spray application at industrial sites will be conducted in spray booths. Tradesmen are expected to mainly apply the coatings using brush and roller.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storages	10-20	4-8	10-15
Coating manufacture	4-8	8	50
QA/Laboratory	2	1	50
Application - Industrial	100	8	200
Application - Tradesmen	> 1000	8	200

EXPOSURE DETAILS

Coating formulation

Dermal and ocular exposure of workers to the notified chemical at concentrations < 10% may occur when manually weighing, connecting and disconnecting pumps, and charging the blending vessels. Dermal and ocular exposure of workers to < 0.1% concentrations of the notified chemical may occur when sampling from the blending vessel, during routine cleaning and maintenance of equipment, and cleaning up of spills or leaks.

Dermal and ocular exposure will be lowered by the use of local exhaust ventilation in the weighing and charging areas and workers wearing personal protective equipment (PPE) such as safety glasses, coveralls, and gloves.

Inhalation exposure of workers to vapours and aerosols of the notified chemical (< 10%) may also occur during blending. Such exposure is expected to be lowered by the local exhaust ventilation employed in areas where weighing and charging of the blending vessels occurs.

Coating application

Dermal and ocular exposure of workers to the notified chemical at < 0.1% may occur during the manual addition of coating to spray guns, during spray application, brush and roller application and when cleaning equipment. Inhalation exposure may also occur during spraying.

Dermal and ocular exposure to the notified chemical (< 0.1%) will be lowered by the use of eye protection, coveralls, and gloves. Inhalation exposure will be lowered by conducting spray operations within spray booths with local exhaust ventilation/extraction. Air respirators will also be used if deemed necessary.

Once dried and cured, the notified chemical is not expected to be bioavailable and dermal contact should not lead to exposure.

6.1.2. Public exposure

Coating products containing the notified chemical at < 0.1% will be available to DIY users. They are expected to apply the coatings using brush or roller. Equipment will be rinsed with water. The main routes of exposure will be dermal and ocular.

The general public may also be exposed to substrates coated with the notified chemical (< 0.1%). However, once dried and cured the notified chemical is not expected to be significantly bioavailable and dermal contact should not lead to significant exposure.

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	LD50 = 175 mg/kg bw; toxic
Rat, acute dermal toxicity	LD50 < 2000 mg/kg bw; harmful
Rat, acute inhalation toxicity (24% concentration)	LC50 > 2.2 mg/L/4 hour; not toxic
Rabbit, skin irritation	corrosive
Rabbit, eye irritation	Expected to be corrosive based on skin irritation results
Guinea pig, skin sensitisation –non-adjuvant test.	evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay (1)	evidence of strong sensitisation EC3 = 0.69%
Mouse, skin sensitisation – Local lymph node assay (2)	evidence of strong sensitisation EC3 = 1.05%
Dogs, repeat dose oral toxicity – 28 day range finding study.	NOEL/NOAEL values were not determined. Notified chemical was not palatable at > 2000 ppm
Rats, repeat dose oral toxicity – 90 days	13 mg/kg bw/day males 15 mg/kg bw/day females
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic
Reproductive effects – 2 generation study	No evidence of reproductive effects NOAEL - parental systemic toxicity: 10-45 mg/kg bw/day (entire P and F1 generations) 14-22 mg/kg bw/day (during pre-mating period) NOAEL for neonatal (F1) toxicity: 23-83 mg/kg bw/day.

Toxicokinetics, metabolism and distribution.
Absorption, distribution, metabolism and excretion of the radiolabelled notified chemical were examined in rats following oral dosing. Radioactivity was detectable in blood and plasma following administration, as well as in several organs of the body. It was also found to be extensively metabolised and was not detected unchanged in the urine or feces. Two major metabolites were detected in urine. The radioactivity was predominantly eliminated from the body in the urine (93 – 99%) and a small amount in the feces (3.85 – 6.35%).

The notified chemical is expected to be absorbed by the dermal route and from the respiratory tract based on its relatively low molecular weight, high water solubility and partition coefficient (log Kow > 0). Dermal absorption is confirmed by the effects (including mortalities) noted in the acute dermal toxicity study on the notified chemical. Respiratory tract absorption is suggested by the effects observed in animals during the acute inhalation toxicity study.

Acute toxicity.
The acute oral toxicity of the notified chemical was tested using animals that were administered 4 different doses. On the basis of the observed mortalities, its LD50 was estimated to be between 175 mg/kg bw (1 of 3 animals died) and 550 mg/kg bw (2 of 2 animals died). As such, the notified chemical is toxic via the oral route.

The acute dermal toxicity of the notified chemical was tested in rats, with the LD50 estimated to be < 2000 mg/kg bw (based on mortality in 3 of 5 animals at this dose level). As such, the notified chemical is harmful via the dermal route.

The acute inhalation toxicity of the notified chemical as a liquid aerosol was measured at concentrations of 24%. Signs of toxicity were observed in all animals, though there was no mortality. It was concluded that the LC50 of the notified chemical at 24% was > 2.2 mg/L/4hours. A definitive LC50 for the notified chemical could not be derived from the study. The chemical is expected not to be toxic via inhalation but it could be harmful via inhalation.

Irritation and Sensitisation.
The skin irritation effects of the notified chemical were tested. As a result of 1 hour and 4 hour exposure of rabbits to the notified chemical, severe erythema was observed in several animals towards the latter part of the observation period, remaining at the final 14 day observation. Following the 4 hour exposure, one animal at day 14 displayed necrosis. On the basis of these observed effects, the notified chemical is considered to be corrosive (R34 Causes burns). Considering its corrosive effects on the skin, the notified chemical is also expected to cause serious eye damage. For this reason, an eye irritation test was not conducted.

The potential for skin sensitisation of the notified chemical was evaluated in 2 local lymph node assays (LLNA). The Stimulation Index (SI) for animals treated with the notified chemical exceeded 3 at 1 and 3% in the first study and 3, 10 and 30% in the second study. The EC3 value was determined to be 0.69% and 1.05% respectively and the notified chemical was considered to be a strong skin sensitiser. This was confirmed by the results of a non-adjuvant Buehler test in which 20% of the test animals displayed reactions indicative of skin sensitisation. As the positive response rate exceeded 15%, the test was considered to indicate the skin sensitisation potential of the notified chemical.

Repeated Dose Toxicity.
The repeated dose oral toxicity of the notified chemical was examined in two studies. A 28 day range-finding study was performed using beagle dogs administered the notified chemical in the diet. The main finding of this study was that the notified chemical was of poor palatability when present in the diet of the test animals at greater than 2000 ppm. A 90 day study was also performed using rats administered the notified chemical in drinking water. The main effects observed included reductions in mean body weights and body weight gains, mainly in rats of the high dose group. The NOAEL for this study was determined to be 200 ppm (13 and 15 mg/kg bw/day for males and females, respectively).

Mutagenicity.
The notified chemical was found to be non-mutagenic in a bacterial reverse mutation assay, an in vitro chromosome aberration test in human peripheral blood lymphocytes, and an in vivo mouse bone marrow erythrocyte micronucleus test.

Reproductive Toxicity.
The reproductive toxicity of the notified chemical was examined using a two-generation study in rats administered the notified chemical in drinking water. There were no treatment related effects on reproductive performance in the parental or first generation animals at any dose level. NOAELs for parental systemic toxicity were established as 10-45 mg/kg bw/day for the entire P and F1 generations, and 14-22 mg/kg bw/day for the P and F1 generations during the pre-mating period. The NOAEL for neonatal (F1) toxicity was established as 23-83 mg/kg bw/day.

Health hazard classification
Based on the mortalities in the acute oral and dermal toxicity studies, the corrosive effects observed in the skin irritation study, and the evidence of skin sensitisation in two LLNA studies and one Buehler sensitisation study, the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

R25 Toxic if swallowed
R21 Harmful in contact with skin
R34 Causes burns
R43 May cause sensitisation by skin contact

Dangerous Goods classification
Based on the acute oral toxicity and corrosive effects of the notified chemical, the notified chemical should be classified according to the Australian Dangerous Goods Code (NTC, 2007).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Toxicological studies on the notified chemical indicate that it is toxic via the oral route and harmful via the dermal route, it is corrosive to the skin, causes serious eye damage, and is a skin sensitiser.

Dermal, ocular and inhalation exposure of workers to the notified chemical at the imported concentrations of < 10% may occur during reformulation of coatings. At these concentrations, workers could potentially be at risk of corrosion/irritation and skin sensitisation. The use of engineering controls (particularly local exhaust ventilation) and personal protective equipment (skin and eye protection) during the reformulation of coatings is expected to minimise exposure and reduce the risk of such effects.

Dermal, ocular and inhalation exposure of workers to the notified chemical at concentrations < 0.1% may occur during coating application (spray, brush or roller). At these low concentrations, the risk of adverse health effects from the notified chemical is not expected. The engineering controls, such as spray booths, and personal protective equipment, such as gloves and overalls, expected to be used during application of coatings should further minimise the risk.

In conclusion, the occupational health and safety risk associated with the notified chemical is not considered to be unacceptable when engineering controls (including local exhaust ventilation) and PPE (skin and eye protection) are used during reformulation of coatings.

6.3.2. Public health

DIY users may be exposed to the notified chemical at concentrations < 0.1% via the dermal or ocular routes. At these low concentrations, adverse health effects of the notified chemical are not expected to occur to a significant extent.

The general public may also be exposed to substrates coated with the notified chemical (< 0.1%). However, the notified chemical will be dried and cured and is not expected to be significantly bioavailable.

In conclusion, the risk to public health associated with the notified chemical 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 imported notified chemical will be reformulated and decanted into end-use containers in Australia. The notified chemical is anticipated to be released as accidental spills (≤1% of annual introduction volume), or as residue (≤1%) remaining in transport containers. Washings from the cleaning of blending equipment will be collected and recycled into the next batch of coating products, although it is estimated that some may be released to sewer (≤0.2%). Notified chemical residues in empty import containers are expected to be sent to landfill with the container, or thermally decomposed during drum recycling.

RELEASE OF CHEMICAL FROM USE

Up to 80% of the formulated coatings containing the notified chemical are expected to be applied in industrial settings to various substrates including wood, furniture and automobiles. The coatings will be applied primarily by spray in spray booths, but also by brush and roller. Overspray is anticipated to account for up to 30% of the annual introduction volume, depending on the size and shape of the article being sprayed. This is likely to be captured by standard engineering practices and, after being allowed to cure, disposed of to landfill. Application equipment from industrial use may be cleaned with water, and an estimated 0.2% of the import volume of notified chemical may be released to sewer.

The remaining 20% of the formulated coatings will be available to the domestic market. During domestic use, the coatings are expected to be applied mainly by brush and roller. It has been estimated that between 10 and 15% of paint remains unused by householders at the end of a job. Much of this may be used for subsequent

jobs but it is estimated that residue in used paint cans will account for approximately 3% (i.e. 0.15 × 20%) of the paint containing the notified chemical. Incorrectly disposed of paint from waste and washing of equipment may be released to sewer, drains or ground. It is estimated that 5% of paint used by do-it-yourself (DIY) practitioners will be released to sewers. Therefore, under this scenario, 1% (0.05× 20%) of the annual import volume of the notified chemical is assumed to be released to sewer annually from the domestic use of coatings containing the notified chemical.

Residual product in end-use containers is expected to be thermally decomposed during metal drum recycling or disposed of to landfill with the used containers.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical is expected to share the fate of the substrate to which it has been applied. Notified chemical in coatings applied to metal articles will be either thermally decomposed during metal recycling at the end of the substrate's useful life, or disposed of to landfill. Cured coating removed by physical means (e.g. sandpaper/scraping) and non-metal articles at the end of their useful life are expected to be disposed of to landfill.

7.1.2 Environmental fate

The majority of the notified chemical will be contained within a dry cured film of the coatings and is not expected to be readily bioavailable. However, the notified chemical is not covalently bound to the coating matrix, and may slowly migrate to the surface of the coatings and leach into surrounding media. As the notified chemical is moderately volatile it may partition to air, and the half-life of the notified chemical in air was calculated to be ≤4.75 h, based on reactions with hydroxyl radicals over a 12 hour day. No ozone reaction was estimated (AOPWIN, v1.92; EPISuite, US EPA 2009). The notified chemical is therefore not expected to persist in the air compartment.

The notified chemical is water soluble and is mobile in soil and sediment. In the case where the notified chemical may leach into water, there is potential for the notified chemical to infiltrate into ground water. However, due to its inherent biodegradability in addition to the dispersed nationwide use of coated articles, significant quantities of notified chemical in ground water are not expected.

Up to 1.4% of the notified chemical is expected to be released to sewer from the washing of reformulation and application equipment and incorrect disposal of unused products. In sewage treatment plants, the notified chemical is not expected to adsorb to sludge, based on its low adsorption coefficient, but is predicted to be removed from influent by up to 41% through inherent degradation (SimpleTreat; European Commission, 2003). If released to surface waters, the notified chemical is expected to disperse and degrade. A small proportion of notified chemical may be applied to land when effluent is used for irrigation. It is not likely to bioaccumulate, based on its low molecular weight, water solubility and inherent biodegradability.

Coated articles at the end of their useful life are expected to be disposed of to landfill or sent for metal reclamation. In landfill, the notified chemical is expected to be mobile, although it is expected to degrade biotically or abiotically to form water and oxides of carbon, nitrogen and sulphur.

For the details of the environmental fate studies, refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

The following Predicted Environmental Concentration (PEC) has been calculated for a worst case scenario assuming that up to 1.4% of the imported quantity of notified chemical is released to sewer from the washing of equipment and incorrect disposal of the formulated product, and that up to 41% is removed from waste water by sewage treatment plant (STP) processes before discharge to surface waters on a nationwide basis.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	40,000	kg/year
Proportion expected to be released to sewer	1.4%	
Annual quantity of chemical released to sewer	560	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	1.53	kg/day
Water use	200.0	L/person/day

Population of Australia (Millions)	21.161	million
Removal within STP	41%	**Mitigation**
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.21	µg/L
PEC - Ocean:	0.02	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.213 µg/L may potentially result in a soil concentration of approximately 1.42 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 7.1 µg/kg and 14.2 µg/kg, respectively. However, given the inherent biodegradability of the notified chemical, these concentrations should be considered as maximum values only.

Extension application
The proposed change to introduction volume (increasing volume from 20 tonne/year to 40 tonne/year) of the notified chemical affects the PEC concentrations calculated in the original assessment. The PEC calculations above were revised to reflect the higher volume.

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*
Acute		
Fish Toxicity - freshwater	96 h LC50 = 0.24 mg/L	very toxic to freshwater fish
Fish Toxicity - saltwater	96 h LC50 = 1.5 mg/L	toxic to marine fish
Daphnia Toxicity	48 h EC50 = 0.92 mg/L	very toxic to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 0.33 mg/L	very toxic to algae
Inhibition of Bacterial Respiration	3 h EC50 = 13.0 mg/L	harmful to microbial respiration
Chronic		
Daphnia Toxicity	21 d NOEC = 0.42 mg/L	toxic with long lasting effects
Algal Toxicity	72 h NOEC = 0.068 mg/L	very toxic with long lasting effects

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is very toxic to freshwater fish, aquatic invertebrates and algae, and toxic to marine fish and is formally classified as 'Acute Category 1; Very toxic to aquatic life'. On the basis of its chronic toxicity to algae, and as the notified chemical has not been demonstrated to be readily biodegradable, the notified chemical is formally classified under the GHS as 'Chronic Category 1; Very toxic with long lasting effects'.

Based on the acute and chronic aquatic toxicity of the notified chemical, it is classified as follows according to the Australian Dangerous Goods Code (NTC, 2007):

Class 9 Environmentally hazardous substances (aquatic environment)

7.2.1 Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated using the endpoint for the most sensitive trophic level (72 h algae NOEC) and an assessment factor of 50, as chronic endpoints for two trophic levels and acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Alga).	0.068	mg/L
Assessment Factor	50	
PNEC:	1.36	µg/L

7.3. Environmental risk assessment

The risk quotient (Q = PEC/PNEC) has been calculated in the table below.

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.21	1.36	0.15
- Ocean:	0.02	1.36	0.015

The notified chemical is acutely and chronically toxic to aquatic organisms, although it is unlikely to reach ecotoxicologically significant concentrations in riverine environments based on its annual importation quantity and the partial removal of the chemical from waste water. The notified chemical has a low potential for bioaccumulation and is unlikely to persist in surface waters. Therefore, at the maximum annual importation volume, the notified chemical is not considered to pose an unacceptable risk to the environment based on the reported use as an in-can preservative for water-based paints.

Extension application

The proposed change to introduction volume (increasing volume from 20 tonne/year to 40 tonne/year) of the notified chemical is not impacting the outcomes of the original environmental risk assessment. The risk quotient calculations above were revised to reflect the higher volume. Therefore, the increase in the maximum annual importation volume of the notified chemical is not considered to pose an unacceptable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 53.3°C

Method OECD TG 102 Melting Point.
Differential Scanning Calorimetry
Test Facility Covance Laboratories Ltd. (2009a)

Boiling Point 324.6°C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Differential Scanning Calorimetry
Test Facility Covance Laboratories Ltd. (2009a)

Density 1452.7 kg/m^3 at 20°C

Method OECD TG 109 Density of Liquids and Solids.
Gas comparison pycnometer
Test Facility Covance Laboratories Ltd. (2009b)

Vapour Pressure 4.249×10^{-5} kPa at 25°C
2.342×10^{-5} kPa at 20°C

Method OECD TG 104 Vapour Pressure.
Knudsen effusion technique (performed at temperatures of 15 - 30 °C)
Test Facility Covance Laboratories Ltd. (2009a)

Water Solubility 14.63 to 15.97 g/L at 20.1°C, pH = 3.5 to 7.8

Method OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Shake Flask Method with HPLC-UV Analytical Method. There were no reported deviations to protocol. The water solubility was found to be 10.35 g/L at 7.8°C and 38.57 g/L at 35°C, pH unadjusted.
Test Facility Covance Laboratories Ltd. (2009a)

Hydrolysis as a Function of pH $t_{½} \geq 1$ year at 25°C

Method OECD TG 111 Hydrolysis as a Function of pH.

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

Remarks There were no reported deviations to protocol. Hydrolysis was <10% after 5 days at pH 4, 7 and 9, and therefore $t_{½} \geq 1$ year at 25°C, indicating the notified chemical is hydrolytically stable under environmental conditions.
Test Facility Brixham Environmental Laboratory (2007a)

Partition Coefficient (n-octanol/water) log K_{OW} at 20°C = 1.4, pH unadjusted

Method OECD TG 117 Partition Coefficient (n-octanol/water), HPLC Method.
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks There were no significant deviations from protocol. The notified chemical was extrapolated to have a partition coefficient of log K_{OW} 1.4 and 1.5, when determined under buffered conditions of pH 8.0 and pH 3.4, respectively.

Test Facility Covance Laboratories Ltd. (2009a)

Surface Tension 60.8 mN/m at 19.8°C

Method OECD TG 115 Surface Tension of Aqueous Solutions
Remarks There were no significant deviations from protocol. The concentration of the test substance was 1.0 g/L.
Test Facility Covance Laboratories Ltd. (2007)

Adsorption/Desorption – main test log K_{OC} = 2.0 to 2.3 at 20°C

Method OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method.

Soil Type	*Organic Carbon Content (%)*	*pH*	*Koc*	*log Koc*
SPH Silt Loam	3.2	6.3	127.31	2.10
Clay	2.0	8.2	117.45	2.07
Loam	17.2	6.8	222.69	2.35
Sandy Loam	2.8	7.3	105.75	2.02
Sediment	0.9	7.3	191.37	2.28

Remarks There were no significant deviations to protocol. The soil system classification was not reported although the sediment and SPH silt loam were obtained from Pennsylvania USA, and the clay, loam and sandy loam were purchased from a laboratory in North Dakota, USA. The test substance was radiolabeled and levels of radioactivity were determined by liquid scintillation counting (LSC) and analysed by LC/MS. The desorption K_{OC} was for the SPH silt loam, clay, loam, sandy loam and sediment was determined as 99.2, 210.26, 159.43, 101.74 and 133.47 respectively, and the mass balance was found to be 100.4 to 100.7 %, 99.7%, 106.7%, 88.4 to 90.3%, and 97.8 to 98.7%, respectively. The notified chemical is highly mobile in silt loam, clay and sandy loam soils and moderately mobile in loam and sediment (McCall et al, 1980).
Test Facility Rohm and Haas Company (2008)

Dissociation Constant pKa ~ -2

Method OECD TG 112 Dissociation Constants in Water.
Remarks pH- Metric titration. There were no reported deviations from protocol. The dissociation constant of the notified chemical was extrapolated to be -2. The compound is a weak base which is not expected to be ionised in the environmental pH range (4-9).
Test Facility Covance Laboratories Ltd. (2009a)

Flammability Not highly flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Test Facility Covance Laboratories Ltd. (2009c)

Autoignition Temperature > 400°C

Method EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks No autoignition was observed up to 400 °C
Test Facility Covance Laboratories Ltd. (2009c)

Explosive Properties Unlikely to possess explosive properties

Method EC Directive 92/69/EEC A.14 Explosive Properties.
Differential scanning calorimetry
Oxygen balance
Remarks No decomposition exotherms were present in the DSC thermogram.
The oxygen balance (-179.16%) indicates that it may have some potential for explosivity

(though it is close to the potential limit value).
The notified chemical does not contain any known explosophores.
The study authors concluded that the findings from the experimental testing of the thermal properties of the notified chemical should outweigh the theoretical calculations and thus that it is unlikely to possess explosive properties.

Test Facility Covance Laboratories Ltd. (2009c)

Oxidizing Properties Unlikely to possess oxidising properties

Method EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks Expert statement
No decomposition exotherms were present in the DSC thermogram.
There are no functional groups present that are known to be associated with oxidising properties.
The oxygen balance (-198.53%) is within the region where there may be potential for oxidising properties.
The study authors concluded that the findings from the experimental testing of the thermal properties of the notified chemical should outweigh the theoretical calculations and thus that it is unlikely to possess oxidising properties.

Test Facility Covance Laboratories Ltd. (2009c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Pharmacokinetic/toxicokinetic

TEST SUBSTANCE [^{14}C]-notified chemical (notified chemical labeled uniformly on benzene ring)
Specific Activity: 51.70 mCi/g
Radiochemical Purity: 99.1%

METHOD OECD TG 417 Toxicokinetics

STUDY DESIGN AND OBJECTIVE
The objective of this study was to investigate the toxicokinetics of the notified chemical in rats (Sprague-Dawley) following oral administration of the radiolabelled notified chemical. Animals were given single oral doses of 10 mg/kg bw or 100 mg/kg bw or were dosed for 5 consecutive days with oral doses of 10 mg/kg bw) in 0.5% methylcellulose

	Group Number	*No of rats/sex*	*Dose mg/kg bw*	*Radioactivity μCi/kg*	*Sample collection*
Test Groups					
	1	4	10	~1□0	Urine, faeces, tissue, carcasses, blood, plasma
	2	3	10	~100	Blood/plasma
	3	4	100	~100	Urine, faeces, tissue, carcasses, blood, plasma
	4	3	100	~100	Blood/plasma
	5	3	10	~100	Blood, plasma, tissues
	6	4	10/day for 5 days	~100/day	Urine, faeces, tissue, carcasses, blood, plasma
Control Group	7	1	0	0	Urine, faeces, tissue, blood/plasma

RESULTS
High dose animals appeared lethargic. One female animal from Group 4 died during the study period.

Absorption and Distribution:
Radioactivity was detectable in blood and plasma up to 48 hr after the low dose and up to 72 hr after high dose administration. Following high dose administration, females had 2.3 – 2.6 times higher exposure to radioactivity than males. Radioactivity was not significantly bound to the cellular component.

Following high dose administration (96 hours post-dose), detectable levels of radioactivity were found in kidneys, liver, plasma, thyroid, lungs, adrenals, bone marrow, ovaries, heart, brain, muscle and spleen, though all levels were very low.

Metabolism:
Radiolabelled notified chemical was extensively metabolized following a single or multiple doses to the rat. Two major metabolites were detected, together with another four minor components. It was proposed that a thiazolin ring-opening (between sulfur and nitrogen atoms) precursor (not detected in this study) was initially formed, followed by glucuronyl (one major metabolite) or methyl (not detected in this study) conjugations. Further oxidation of the methyl thiol, *N*-demethylation, and hydroxylation resulted in the other detected metabolites of the notified chemical. Radiolabelled notified chemical was not detected unchanged in urine or feces. The metabolite profiles of urine and feces from the multiple oral dose group were similar to those of the single dose group. Overall, the findings indicate that the notified chemical does not bioaccumulate in rat tissues.

Excretion:
After a single dose at 10 mg/kg or 100 mg/kg, or multiple daily doses at 10 mg/kg/day, the majority of radioactivity was recovered in the urine (93.0% to 99.0%, including cage rinse). A small amount of radioactivity was found in the feces (3.85% to 6.35%). There was no apparent gender difference in excretion

patterns or tissue residue levels.

TEST FACILITY XenoBiotic (2009)

B.2. Acute toxicity – oral

TEST SUBSTANCE Notified chemical (>98% purity)

METHOD OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure.
Species/Strain Rat/Wistar albino, 7 females
Vehicle Distilled water.
Test article was warmed in its original container in a water bath, measured amount removed and ground with mortar and pestle and diluted with distilled water to give 20% solution.
Remarks - Method Animals were observed ½, 1, 2 and 4 hours postdose and once daily for 14 days for toxicity and pharmacological effects. All animals were observed twice daily for mortality.

Body weights were recorded pretest, weekly, at death or at termination of study. All animals were examined for gross pathology.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 female	2000	Yes
2	1 female	175	Yes
3	1 female	55	No
4	1 female	175	No
5	1 female	550	Yes
6	1 female	175	No
7	1 female	550	Yes

LD50 175 mg/kg bw
Signs of Toxicity Death occurred by day 1 with predeath physical signs of lethargy, piloerection, ataxia, prostration, flaccid muscle tone, negative righting reflex, few faeces, tremors, wetness of the nose/mouth area and laboured breathing.
Surviving animals showed signs of piloerection, chromorhinorrhea, few faeces and emaciation.

Body weight changes were normal in 2/3 animals. Weight loss was observed in one animal in the second week of observation.
Effects in Organs Necropsy of the animals that died revealed abnormalities of the thymus, kidneys, liver and gastrointestinal tract.

Necropsy results of surviving animals were normal.

CONCLUSION The notified chemical is toxic via the oral route.

TEST FACILITY MB Research Laboratories (2009a)

B.3. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical (>98% purity)

METHOD OECD TG 402 Acute Dermal Toxicity.
Species/Strain Rat/ Wistar albino

	5 males and 5 females dosed at 5000 mg/kg each 5 females dosed at 2000 mg/kg each
Vehicle	Distilled water. Test article was warmed in its original container in a water bath, measured amount removed and ground with mortar and pestle and moistened with 0.1 - 0.2 mL of distilled water.
Type of dressing	Semi-occlusive. The ground test material was placed directly onto an impervious cuff and applied directly to the clipped intact skin. The cuff was moistened with 0.1 – 0.2 mL distilled water to ensure good contact with the skin. The test material remained in contact with the skin for approximately 24 hours at which time the cuff and bandages were removed and the test sites wiped clean with tap water and paper towels.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 male	5000	5 (within 1 day of dosing)
2	5 female	5000	5 (within 1 day of dosing)
3	5 females	2000	3 (within 1 day of dosing)

LD50	<2000 mg/kg bw
Signs of Toxicity - Local	5000 mg/kg bw Necropsy results of dead animals (10) revealed treated skin abnormalities of edema and erythema in one female animal. 2000 mg/kg bw Necropsy results on the dead animals (3) revealed abnormalities of the treated skin. The surviving animals showed erythema, edema, escher and flaking skin. Skin abnormalities were noted in the survivors at every observation point from day 1 to day 14.
Signs of Toxicity - Systemic	5000 mg/kg bw Lethargy, ataxia and tremors were noted in one animal prior to death. 2000 mg/kg bw Two of the five females survived the treatment. Three animals died by day one after treatment and showed physical signs of wetness of the anogenital area and chromodacryorrhea (excessive secretion of red tears). The survivors showed signs of lethargy, wetness of the anogenital area and chromorhinorrhea (wet, red material around nose). Body weight changes in survivors were normal. Body weight changes could not be measured in animals that died, due to their early death.
Effects in Organs	5000 mg/kg bw Necropsy results revealed red areas on the thymus and pancreas, yellow staining of the fatty tissue in the peritoneal cavity posterior to the kidney and intestinal abnormalities. 2000 mg/kg bw Necropsy results on the dead animals (3) revealed abnormalities of the pancreas, thymus and gastrointestinal tract, as well as wetness of the anogenital area.
Remarks - Results	Since two the five animals survived the 2000 mg/kg bw dose, this suggests that the LD50 is slightly below this level. As the test material is a strong irritant and in the interest of conserving animals no further testing was conducted to estimate the actual LD_{50}

CONCLUSION The notified chemical is harmful via the dermal route.

TEST FACILITY MB Research Laboratories (2009b)

B.4. Acute toxicity – inhalation

TEST SUBSTANCE Product containing notified chemical as 24% active ingredient

METHOD OECD TG 403 Acute Inhalation Toxicity – Limit Test.
Species/Strain Rat/Sprague-Dawley
Vehicle Not stated
Method of Exposure Nose-only exposure
Exposure Period 4 hours
Physical Form Liquid aerosol
Particle Size 3.4 μm average Mass Median Aerodynamic Diameter (at the exposure concentration)
Remarks - Method A control group was not tested.
Observation period: 14 days
Air changes per hour in chamber: 21.7
When 99% concentration was attained in the inhalation chamber, animals were transferred to the nose only chamber for 4 hours exposure and then returned to their usual housing for observation.
The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined gravimetrically twice per hour and nominally at the end of the exposure.

RESULTS

Number and Sex of Animals	*Concentration <mg/L>*			*Mortality*
	Nominal	*Actual*	*Range*	
5M, 5F	5.38	2.2	2.040 – 2.485	0

LC50 > 2.2 mg/L/4 hours for 24% notified chemical
Signs of Toxicity All animals displayed piloerection (slight to very slight) and activity decrease. All males and one female displayed respiratory chirp. No effects were seen from day 8 onwards.
Body weight gain was affected, with four animals losing, or not gaining weight during the first week.
Effects in Organs No abnormalities were observed at gross necropsy.

CONCLUSION The notified chemical at 24% is expected to be not toxic via inhalation. According to the Approved Criteria (NOHSC, 2004), LC50 ≤ 5 mg/L/4hr is considered to be harmful by inhalation. This study cannot be used to derive a definitive LC50 for the notified chemical.

TEST FACILITY Stillmeadow (2009)

B.5. Irritation – skin

TEST SUBSTANCE Notified chemical (purity >98%)

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3 females
Vehicle Distilled water.
Test article was a yellow solid which was warmed in its original container in a water bath, measured amount removed and ground with mortar and pestle and moistened with 0.1 ml of distilled water.

Observation Period	24, 48 and 72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	One animal was treated with a dose of 0.5 g of the test substance for 3 minutes. Since no evidence of a corrosive effect was observed, two additional animals were added to the study. All three animals were treated for 1 hour and 4 hours. All applications were to different sites. Only the 4 hour treatment results are discussed here.

RESULTS

One hour exposure

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1	0.67	0.67	4 (7 days)	14 days	>4
Oedema	1.33	1.67	1.33	3 (1 hour)	14 days	0

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

Four hour exposure

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1.33	1.33	1.33	4 (7 days)	14 days	>4
Oedema	2	2	1.67	3 (1 hour)	14 days	1

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

Remarks - Results

1-hour exposure: Very slight erythema and moderate edema was observed at 60 minutes following the one hour xposure. Absent to well defined erythma and very slight to slight edema was observed at 24 hours. Absent to very slight erythema, with pale areas on 2 animals, and very slight to slight edema was observed at 48 and 72 hours. By day 7 and 14, erythema progressed to severe for 2 out of 3 animals and remained very slight for one animal with dark areas on day 7. Poor hair regrowth was also noted in this animal on day 14. All animals were noted with flaking skin on day 14. Edema was very slight on day 7 and absent on day 14. Test substance residue was noted on one animal through 24 hours and in another aanimal through 72 hours.

4-hour exposure: Well defined erythema and moderate edema was observed at 60 minutes following the 4 hour exposure. Very slight to well defined erythema with pale and dark areas were noted at 24, 48 and 72 hours. Slight edema was observed at 24 and 48 hours. Very slight to slight edema was noted at 72 hours. By Day 7, erythema progressed to severe for all animals with slight edema. By Day 14, one animal was observed with necrosis and one with moderate eschar and all animals had flaking skin. Edema was absent to very slight on Day 14. Test substance residue was noted in all animals through 72 hours.

There were no abnormal physical signs of systemic effects during the duration of the study.

Body weight changes were normal for all three animals.

CONCLUSION The notified chemical is corrosive to the skin.

TEST FACILITY MB Research Laboratories (2009c)

B.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 406 Skin Sensitisation – non-adjuvant Buehler test.
Species/Strain	Guinea pig/Hartley Albino
PRELIMINARY STUDY	Not performed
MAIN STUDY	
Number of Animals	Test Group: 30 Control Group: 25
INDUCTION PHASE	Induction Concentration: Topical: 600, 1200, 1800 ppm
Signs of Irritation	No irritation was observed
CHALLENGE PHASE	
1st challenge	topical: 600, 1200, 1800 ppm
2nd challenge	topical: 1800 ppm
Remarks - Method	A total of nine 6-hour induction exposures were performed (3 times per week over a 3-week period).

RESULTS

Animal	*Challenge Concentration (ppm)*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	600	0/10	0/10	-	-
	1200	0/10	0/10	-	-
	1800	2/10	0/10	2/2	0/2
Negative Control Group	600	0/10	0/10	-	-
	1200	0/10	0/10	-	-
	1800	0/10	0/10	0/3	0/3
Positive Control Group*	50% in acetone	3/10	3/10	-	-

*α-hexylcinnamaldehyde

CONCLUSION	According to the OECD test guideline, a response of at least 15% is considered to be positive in a non-adjuvant skin sensitisation test. Thus under the conditions of this test, evidence of reactions indicative of skin sensitisation to the notified chemical (20% response) were observed.
TEST FACILITY	MB Research (2009d)

B.7. Skin sensitisation – mouse local lymph node assay (LLNA) (1)

TEST SUBSTANCE	Notified chemical (> 98% purity)
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)
Species/Strain	Mouse/CBA/J
Vehicle	Acetone/Olive oil (4:1)
Remarks - Method	No significant protocol deviations

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	26834	-
0.1	28474	1.1
0.3	70073	2.6
1.0	88831	3.3
3.0	200971	7.5
Positive Control		
25		

Remarks - Results

Residues of the test substance were observed on the ears of 2 animals in the group treated with 3%. However, the residues did not interfere with ear measurements.
Ear swelling measurements indicated that the notified chemical was a skin irritant at the highest concentration tested (3%).
The notified chemical elicited a proliferative response from the auricular lymph nodes indicative of skin sensitisation. A dose response was observed and the stimulation index (SI) was greater than 3 for animals treated with the notified chemical at 1% and 3%. The EC3 value was determined to be 0.69%.
The positive control test found HCA to induce a SI of 8.8 at 25% concentration, thus confirming the acceptability of HCA as a reliable positive control substance.

CONCLUSION

There was evidence of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY

MB Research Laboratories (2009e)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA) (2)

TEST SUBSTANCE

Notified chemical (> 98% purity)

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse/CBA/Ca

Vehicle: Acetone/Olive oil (4:1)

Remarks - Method: The study on the positive control was conducted more than 6 months prior to this study. However, this is not considered to significantly affect the outcome of the study. No other significant protocol deviations.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1206	-
0.3	2391	2.0
1	3466	2.9
3	8770	7.3
10	12556	10.4
30	18942	15.7
Positive Control		
10	3964	3.9
23	9780	9.6
43	15149	14.9

Remarks - Results	Residues of the notified chemical were noted on and around the ears of mice treated with the notified chemical at 30%. The notified chemical elicited a proliferative response from the auricular lymph nodes. A dose response was observed and the stimulation index (SI) ≥ 3 for animals treated with the notified chemical at 3%, 10% and 30%. The EC3 value was determined to be 1.046%. The positive control test found HCA to induce a SI of 3.9, 9.6 and 14.9 at concentrations of 10, 23 and 43% respectively, thus confirming the acceptability of HCA as a reliable positive control substance.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Charles River Laboratories (2008)

B.9. Repeat dose toxicity, 28 days - Dogs

TEST SUBSTANCE	Notified chemical (> 98% purity)
METHOD	Range finding study similar to OECD TG 409 Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents.
Species/Strain	Dog/Beagle
Route of Administration	Oral –diet
Exposure Information	Total exposure days: 28 Dose regimen: 7 days per week Post-exposure observation period: Nil
Vehicle	Acetone
Remarks - Method	Test diet mixtures containing the notified chemical were offered to animals for 4 hours per day. Some of the test groups were fed basal diet for a few days during the test period, returning to the test diet mixtures with lower concentrations of the notified chemical (due to palatability issues that resulted in low food consumption – see below).

RESULTS

Test Group	*Number and Sex of Animals*	*Test Diet Concentration <ppm*>*				*Mortality*
		Week 0	*Week 1[α]*	*Week 2*	*Week 3*	
1	2M, 2F	0	0	0	0	0
2	2M, 2F	2000	2000	2000	2000	0
3	2M, 2F	4000	1000	1000	1000	0
4	2M, 2F	8000	3000	500	2500	0

* Dietary concentrations were not adjusted for body weight or test substance purity.

[α] The test substance was poorly palatable at dietary concentrations of 3000, 4000 and 8000 ppm. As a result, test groups 3 and 4 were returned to the basal diet for days 3 – 6, and test group 4 was additionally returned to the basal diet for days 9 – 13. Both groups were returned to test diets at the beginning of the following week after revision of the test substance dietary concentrations.

Clinical Observations

Lower body weights, lower body weight gains, and corresponding decreased food consumption were observed in many of the animals at the higher dose levels. This was considered to be related to poor palatability of the diet when containing the notified chemical at concentrations above approximately 2000 ppm. When animals were returned to the basal diet, immediate increases in food consumption to a level comparable to controls were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Potentially test substance-related, lower white blood cell and reticulocyte counts compared to the control group were noted in the Group 4 males at the study week 4 evaluation. The reductions were also dose-related.

Mean and individual white blood cell and reticulocyte counts in these animals were also noted to be lower compared to their respective pretest values. The significance of these findings is uncertain, as no other remarkable erythrocyte or leukocyte alterations were noted and there was no similar effects observed in females.

CONCLUSION
The notified chemical was not palatable at test diet concentrations greater than 2000 ppm. No overt signs of toxicity were observed at the dietary concentrations used in this study. A No Observed (Adverse) Effect Level (NO(A)EL) was not established in this study, as it was performed as a range finding study.

TEST FACILITY WIL Research (2009a)

B.10. Repeat dose toxicity, 90 days - Rats

TEST SUBSTANCE Notified chemical (> 98% purity)

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain Rat/Crl:CD(SD)
Route of Administration Oral – drinking water
Exposure Information Total exposure days: 90 or 91
Dose regimen: 7 days per week. Water containing the notified chemical was available ad libitum.
Post-exposure observation period: N/A. Animals were euthanized after the final dose.
Vehicle Water
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*			*Mortality*
		ppm	*Males (mg/kg/day)*	*Females (mg/kg/day)*	
control	10/sex	0	0	0	0/20
low dose	10/sex	50	3	4	0/20
mid dose	10/sex	200	13	15	1/10 M, 0/10 F
high dose	10/sex	800	50	60	0/20

Mortality and Time to Death
One male in the mid dose group was found dead on study day 57. This rat displayed moderate diffuse acute congestion and moderate pulmonary hemorrhage, marked diffuse necrosis of the tracheal mucosa and multifocal hemorrhage in the thymus. These effects may have been due to inadvertent aspiration of the test drinking water and this death was not considered due to direct systemic toxicity of the test substance. In addition, no deaths were observed at higher test substance doses.

Clinical Observations
Test substance-related lower mean body weights and body weight gains were observed in the mid and high dose groups of males and females compared to controls. The magnitude of the body weight decreases was considered by the study authors to be adverse for the high dose group (at the end of the test substance administration period, mean body weights were 13.4% and 6.5% lower than the controls for the high dose males and females, respectively).

Lower mean food consumption was observed in mid and high dose males and high dose females at many of the measured intervals throughout the study. The reduced food consumption was consistent with the observed body weight reductions.

Lower mean water consumption was observed in all male dose groups, and in the mid and high dose females. These effects were considered to be due to the poor palatability of the test substance in the drinking water formulations, rather than systemic toxicity of the test substance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Lower total protein and globulin levels and higher A/G (albumin/globulin) ratio in the mid and high dose group males and higher urea nitrogen and phosphorus levels in the high dose group females were attributed to poor nutritional and/or hydration status.

Effects in Organs
Treatment-related microscopic changes were observed in a few females from the high dose group. The treatment-related changes were observed in both the forestomach and glandular areas of the stomach. These changes were considered to represent an adverse local irritation of the stomach resulting from administration of the test substance.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 200 ppm, which was equivalent to 13 and 15 mg/kg bw/day for males and females, respectively, in this study, based on some mean body weights and body weight gain effects observed at this dose level. Significant body weight gain effects and stomach irritation effects were observed at the high dose level.

TEST FACILITY WIL Research (2009b)

B.11. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (>98% purity)

METHOD
OECD TG 471 Bacterial Reverse Mutation Test.

Species/Strain	Preliminary Test: *S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA Main Test: *S. typhimurium*: TA1537. *E. coli*: WP2 uvrA.
Metabolic Activation System	Aroclor 1254-induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate b) Without metabolic activation: 1.5, 5.0, 15, 50, 150 and 500 µg/plate
Vehicle	Dimethyl sulfoxide (DMSO).
Remarks - Method	No deviations from standard operating procedures. Each concentration was tested in triplicate. Evaluating the mutagenic potential of the test substance by measuring its ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and at the tryptophan locus of Escherichia coli strain WP2uvrA in the presence and absence of Aroclor-induced rat liver S9.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				

Test	≥150	*(S. typhimurium*: TA1537 and WP2 uvrA) ≥150	0	Nil
Present				
Test	≥150	*(S. typhimurium*: TA1537 and WP2 uvrA) ≥500	0	Nil

Remarks - Results

In the preliminary toxicity mutation assay, the maximum dose tested was 5000 µg/plate and no positive response or precipitate were observed. The dose levels tested were 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate. Toxicity was observed beginning at 150 or 500 µg/plate. Based on the findings of the preliminary toxicity mutation assay the maximum doses plated in the main mutagenicity assay were 1500 µg/plate with TA1537 and WP2 uvrA in the presence of S9 activation and 500 µg/plate in the absence of S9 activation.

In the main mutagenicity assay, no positive mutagenic response and no precipitate was observed. The dose levels tested were 5.0, 15, 50, 150, 500 and 1500 µg/plate with TA1537 and WP2 uvrA in th the presence of S9 activation and 1.5, 5.0, 15, 50, 150 and 500 µg/plate in the absence of S9 activation. Toxicity was observed beginning at 150 µg/plate in the absence of S9 activation and beginning at 500 µg/plate in the presence of S9 activation .

The positive control 9-aminoacridine at 75 µg/plate was used for TA1537 strain and methyl methanesulfonate at 1000 µg/plate for WP2 uvrA strain. The mean of each positive control for each tester strain exhibited at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control.

CONCLUSION

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

TEST FACILITY

BioReliance (2006a)

B.12. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical (>98% purity)

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line: Human peripheral blood lymphocytes (HPBL)
Metabolic Activation System: Aroclor 1254-induced rat liver S9 (from Sprague-Dawley rats)
Vehicle: Dimethyl sulfoxide (DMSO).
Remarks - Method: The chromosome aberration assay performed using standard procedures. (Statistical analysis of the percent aberrant cells was performed using Fisher's exact test).

No known deviations from the protocol or assay

A preliminary toxicity test was performed to establish the dose range for testing in the cytogenetic test. The chromosome aberration assay was used to evaluate the clastogenic potential of the notified chemical. Mitomycin (MMC) was used as the positive control in the non-activated study at final concentrations of 0.3 and 0.6 µg/mL. Cyclosporin (CP) was used as the positive control in the S9-activated study at final concentrations of 20 and 40 µg/mL.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*	*Cells with Aberrations (%)*	
				Numerical	Structural
Absent					
Test 1	0.625, 1.25, 2.5*, 5.0*, 7.5, 10*, 12.5, 15	4 h	20 h	0.0	0.0**
Test 2	0.625, 1.25, 2.5*, 5.0*, 7.5, 10*, 12.5, 15	20 h	20 h	0.0	0.5***
Present					
Test 1	0.625, 1.25, 2.5*, 5.0*, 7.5, 10*, 12.5, 15	4 h	20 h	0.0	1.0****

*Cultures selected for metaphase analysis.
** Mitomycin C 0.6 µg/mL produced 15% structural aberrations.
*** Mitomycin C 0.3 µg/mL produced 17% structural aberrations.
**** Cyclosporin 20 µg/mL produced 14% structural aberrations.

Remarks - Results

In the preliminary toxicity assay, the maximum dose tested was 1650 µg/ml on Human peripheral blood lymphocytes in the absence and presence of Aroclor-induced S9 activation system for 4hours and continuously for 20 hours in the absence of S9 activation. The test substance was soluble in DMSO and in the treatment medium at all concentrations at the beginning and end of the treatment period. At the end of the treatment period, hemolysis was observed at dose levels ≥49.5 µg/mL in all treatment groups. Selection of dose levels for the chromosome aberration assay was based on a reduction in the mitotic index relative to the solvent control. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at dose 16.5 µg/mL in all three exposure groups. Based on these findings, the doses chosen for the chromosome aberration test ranged from 0.625 to 15 µg/mL for all three treatment groups.

In the chromosome aberration assay, the cells were treated for 4 and 20 hours in the S9 non-activated test system and 4 hours in the presence of S9 activated test system. All cells were harvested 20 hours after treatment initiation. The test substance was soluble in DMSO and in the treatment medium at all concentrations tested at the beginning and end of the treatment period. Selection of doses for microscopic analysis was based on mitotic inhibition (the lowest dose with at least 50% reduction in mitotic index, relative to the solvent control and two lower doses) in all harvests.

The percentage of cells with structural or numerical aberrations was not significantly increased in the test-substance groups over the solvent control groups ($p>0.05$, Fisher's exact test).

CONCLUSION

The notified chemical was not clastogenic to Human peripheral blood lymphocytes, treated in vitro under the conditions of the test.

TEST FACILITY

BioReliance (2006b)

B.13. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical (> 98% purity)

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.

Species/Strain: ICR Mice
Route of Administration: Oral – gavage
Vehicle: 0.5% Methylcellulose/0.1% Tween 80 in purified water

Remarks - Method A preliminary dose range-finding study was performed using doses of 50, 100, 200 and 300 mg/kg in 5 mice/sex/group.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	10/sex	-	5/sex 24 hr; 5/sex 48 hr
II (low dose)	5/sex	50	24 hr
III (mid dose)	5/sex	100	24 hr
IV (high dose)	10/sex*	200	5/sex 24 hr; 5/sex 48 hr
V (positive control, CP)	5/sex	5	24 hr

CP=cyclophosphamide.
*An additional 5 animals/sex were dosed

RESULTS

Doses Producing Toxicity

Range-finding study
Mortality was observed in 1/5 females at 200 mg/kg; 4/5 males and 1/5 females at 300 mg/kg.
Piloerection was observed in all mice at all doses. Lethargy was observed in all mice at 200 and 300 mg/kg. Hunched position and palpebral closure was observed in all animals at 300 mg/kg. Crusty eyes were observed in 2/5 males and 1/5 females at 200 mg/kg. At 300 mg/kg, 4/5 males and 2/5 females were cool to the touch. There also appeared to be some reductions in mean body weights at the higher doses. Based on the results of this study, 200 mg/kg was chosen as the highest dose for the main study.

Main study
Mortality was observed in 1/15 males and 2/15 females at 200 mg/kg.
Piloerection was observed in all mice at all doses. Lethargy was observed in all mice at 200 mg/kg.

Genotoxic Effects

Reductions in the PCEs/ECs (polychromatic erythrocytes/total erythrocytes) ratio up to 29%, were observed in the 24 hour male test groups relative to the control group. No appreciable reductions in the PCEs/ECs ratio were seen in the 24 hour female group (0.7%). No reductions in the PCEs/ECs ratio was observed in the 48 hour male and female test groups. The magnitude and lack of dose dependency of the reductions suggest that the test article did not inhibit erythropoiesis.

No statistically significant increases in the incidence of micronucleated polychromatic erythrocytes were observed in animals treated with the test substance relative to controls at 24 or 48 hours after dose administration.

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

TEST FACILITY BioReliance (2009)

B.14. Toxicity to reproduction – two generation study

TEST SUBSTANCE Notified chemical (> 98% purity)

METHOD OECD TG 416 Two-Generation Reproduction Toxicity Study

Species/Strain Rat/ Crl:CD(SD)

Route of Administration Oral – drinking water

Exposure Information Exposure period – female (P and F1): 70 days prior to mating; during mating, gestation, lactation and then until euthanasia.

Exposure period – male (P and F1): 70 days prior to mating, during mating and then until euthanasia.

	Dose regimen: ad libitum (24 hours, 7 days per week); Dose levels: 0, 50, 200 and 800 ppm: high dose reduced to 400 ppm in week 16 due to toxicity.
Vehicle	Water
Remarks - Method	No significant protocol deviations

Weeks on study	*P*	*F_1*	*F_2*
1	Animals 8 weeks old at start of dosing schedule.		
10-12	P generation mating period – pairing to produce F_1 litters.		
		8 pups per litter (4 per sex, when possible) were selected on post natal day 4	
18		Commencement of test substance exposure	
16	Reduction of 800 ppm exposure group to 400 ppm.		
29-31		F1 mating period	
			8 pups per litter (4 per sex, when possible) were selected on post natal day 4

Generation	*Group*	*Number and Sex of Animals*	*Dose/Concentration <units>*					
			Nominal (ppm)	*Actual (mg/kg/day)*				
				Males before mating	*Males after mating*	*Females before mating*	*Females gestation*	*Females lactation*
P								
	I	30 per sex	0	-	-	-	-	-
	II	30 per sex	50	4	3	5	5	11
	III	30 per sex	200	14	10	19	23	44
	IV	30 per sex	800/400[A]	50	40/20	59	64	113/76
F_1								
	I	30 per sex	0	-	-	-	-	-
	II	30 per sex	50	5	3	6	6	11
	III	30 per sex	200	18	11	22	21	45
	IV	30 per sex	400	39	23	44	41	83

[A] Dose reduced to 400 ppm at study week 16

RESULTS

Mortality and Time to Death

Four parental (P) animals were euthanized *in extremis* or found dead during the study (one control female, one 200 ppm treated male, one 200 ppm treated female and one 800/400 ppm treated male), however there was no dose response and the deaths were not considered substance related. All other P and F_1 parental animals survived to the scheduled necropsies.

Effects on Parental (P) animals:

Females of the 800/400 ppm group displayed increased incidences of red and yellow material on various body

surfaces, primarily during the period of exposure to 800 ppm. Several females in this group also displayed an unkempt appearance during lactation. These findings were considered to be due to test substance exposure.

Males of the 800/400 ppm group displayed lower body weight gains throughout exposure to 800 ppm. This generally corresponded to lower mean food consumption. Following reduction to 400 ppm, mean body weight gains were slightly higher in these males than the controls.

During gestation and lactation, females in the 800/400 ppm group had lower mean body weights than controls. Mean food consumption was lower for females in this group during some of the gestation days. During the overall lactation period, mean food consumption was lower than controls, though there were variations that corresponded to the dose reduction, etc.

Dose related reductions in mean water consumption were observed in all dose groups, mainly in male animals. These effects were considered to be due to the poor palatability of the test substance and were only considered by the study authors to be severe at the high dose level (ie. when associated with decreased body weights). There were also some reductions in mean water consumption during gestation and lactation and these were mainly of statistical significance in the high dose group.

No treatment related effects on reproductive performance (estrous cycles, mating, fertility, copulation and conception indices, the mean number of days between pairing and coitus and the mean length of gestation), parturition and the mean numbers of former implantation sites and unaccounted-for sites. No treatment related effects were observed on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, motility and the percentage of morphologically normal sperm). In addition, there were no microscopic changes in reproductive tissues that were considered to be treatment related.

In females of all treatment groups of P, there was a dose related increase in absolute and relative kidney weights compared to controls (statistically significant for the mid and high dose groups). However, in the absence of the corresponding observation in F1 females, this effect was not considered to be related to treatment.

Focal papillary edema was observed in the kidneys of 3/30 males and 5/30 females of the high dose groups of P. This is not a common finding amongst laboratory animals generally and was not observed in lower dose animals

Effects on 1st Filial Generation (F1)

Some pups in the high dose group displayed uneven hair growth and unkempt appearance on post-natal days 14 and/or 21. In addition, a pale body was noted for 8 pups (3 litters) from the high dose group, with most of these pups subsequently being found dead or missing. A number of pups were found dead or missing or were euthanized due to lack of body weight gain. These pups did not display any findings that were considered to be test substance-related.

Mean male and female body weights of the high dose group tended to be lower than controls.

In the high dose group, lower mean absolute and relative spleen and thymus weights and absolute brain weights were observed. These were attributed to the lower body weights caused by the test substance.

A slight delay in the mean attainment age of balanopreputial separation was observed in high dose males. The mean body weight at the age of attainment was found to be statistically significantly lower than the control group. This was believed to be due to the test substance-related decreased mean body weights of this group.

A delay was observed in the mean age of attainment of vaginal patency in females of the high dose group and the mean body weight at this age was statistically significantly lower than the controls. This was thought to be due to the test substance-related decreased mean body weights of this group.

There were some lower mean body weights than controls mainly during lactation in females of the mid and high dose group. In the mid dose group, this was only statistically significant for a short time (lactation days 1-4) during the lactation period, though not for the overall period (days 1-21). The changes were of statistical significance in the high dose group during lactation for days 1-4 and 7-14 and also for the overall lactation period. There were also some reductions in mean food consumption in the high dose group that tended to correspond to decreases in body weight.

There were dose dependent reductions observed in water consumption. These tended to be associated with decreased body weights when observed in the mid and high dose groups and were believed to be due to the poor palatability of the test substance.

No test substance related effects on reproductive performance were observed at any dose level.

There were some changes in organ weights that were considered to be due to the observed reduced body weights.

Focal papillary edema of the kidneys was observed in 4/30 males in the high dose group, with lower incidences in each of the female rats at all dose levels and one control animal. The occurrence in a control animal suggests that the lesion could be an incidental finding, however, the incidence of papillary edema in high dose males and females of the P generation indicates that it may be exposure related.

Effects on 2nd Filial Generation (F2)

Some pups were found dead or missing, though these findings were not considered to be related to test substance treatment.

Pups in the high dose level groups displayed some reductions in body weight compared to controls.

There were some changes in organ weights that were considered to be due to the observed reduced body weights.

Remarks – Results

The authors indicate that the occurrences of focal papillary edema in high dose animals of the P and F1 generation may be associated with dehydration of rats at this exposure level (due to decreases in their water consumption) and the concentration of acidic metabolites of the test substance in the urine.

CONCLUSION

The following No Observed (Adverse) Effect Levels (NO(A)EL) have been reported by the study author for parental reproductive toxicity, parental systemic toxicity and neonatal toxicity.

1. The NOAEL for parental reproductive toxicity (P and F1 generations) was established as 400 ppm based on the lack of effects on reproductive performance at the high dose level. This was equivalent to 40-113 mg/kg bw/day for the P generation during the 800 ppm exposure level, 20-76 mg/kg bw/day for the P generation during the 400 ppm exposure level, and 23-83 mg/kg bw/day for the F1 generation.

2. The NOAEL for parental systemic toxicity (P and F1 generations) was established as 200 ppm based on the changes in body weight, reduced food consumption, the clinical observations (material found on body surfaces and unkempt appearance), and focal papillary edema of the kidneys at the high dose level. This was equivalent to 10-45 mg/kg bw/day for the entire P and F1 generations and 14-22 mg/kg bw/day for the P and F1 generations during the pre-mating period.

3. The NOAEL for neonatal toxicity (F1) was established as 200 ppm (23-83 mg/kg bw/day) based on the body weight changes in animals at the high dose level.

TEST FACILITY WIL Research (2009c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: ^{14}C-labelled notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test (Modified Sturm Test).

Inoculum	Activated sludge from a predominantly domestic sewage treatment works
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The concentration of the test substance was determined by high performance liquid chromatography (HPLC) using UV/visible and radiochemical detection. Liquid scintillation counting (LSC) was used to determine radio specific activity.
Remarks - Method	After a preliminary toxicity test was performed to determine the concentration of the notified chemical which did not inhibit activity of the activated sludge, ^{14}C-labelled notified chemical was tested for its biodegradability potential. The production of $^{14}CO_2$ of inoculated medium containing the ^{14}C-labelled test substance (nominally 389 µg/L and 1 µg/L) was measured over 28 days. Positive controls (reference material, D-[^{14}C(U)]glucose, 1 mg/L) and toxicity controls (test substance and reference material) were run in parallel. The percentage biodegradation is expressed as a ratio of evolved carbon dioxide, corrected for the blank, to the initial theoretical carbon added as test substance. Test conditions were: 22°C ± 2°C, pH 6.9 to 7.1 This study was conducted in compliance with UK and OECD Good Laboratory Practice (GLP) Standards/Principles.

RESULTS

Test substance		*D-[^{14}C(U)]glucose*	
Day	*% Degradation*	*Day*	*% Degradation*
1	<1	1	19
10	<1	10	65
21	<1	21	76
28	<1	28	79

Remarks - Results

Based on the mineralisation of sodium benzoate in the preliminary toxicity test, the results indicated that the test substance was not inhibitory at 10 mg/L, the highest concentration tested. However, a concentration less than an order of magnitude lower was chosen for the main test to avoid any chance of toxicity. The inoculum of the preliminary test was exposed to the test substance for seven days prior to the addition of the degradable substrate, sodium benzoate.

The reference substance employed in the biodegradation study, D-[^{14}C(U)]glucose, is not specified by the OECD guidelines, but was reportedly suitable for this purpose.

More than 60% mineralisation of the reference substance occurred within a 10-day window, thereby confirming that the activated sludge was viable. All other validity criteria were satisfied. The mass balance of the applied radioactivity was present in the test solutions and/or associated with the sludge. Less than 1% test substance was mineralised to $^{14}CO_2$.

CONCLUSION: The notified chemical is not readily biodegradable

TEST FACILITY Brixham Environmental Laboratory (2007b)

C.1.2. Ready biodegradability – degradation products

TEST SUBSTANCE Notified chemical

METHOD OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test (Modified Sturm Test), as per Section C.1.1. above

Remarks – Method This study was conducted for the purpose of identification of degradation products formed during the modified OECD 301B test.

Remarks – Results Whilst negligible mineralisation of the test substance was observed over the 28 day test period, analyses of the inoculated media containing the test substance indicated that the test substance was not present at the end of the study and, therefore, primary degradation was occurring in the system.

HPLC analysis indicated two unknown degradation products were formed at >l0% of the applied radioactivity. Unknown 1 (22 to 28% of the supernatant radioactivity) was tentatively identified as either hydroxy-N-methyl-2-(methy1thio)benzamide or N-methyl- 2-(methylsulfinyl) benzamide (molecular weight 198.06), and unknown 2 (69 to 78% of the supernatant radioactivity) was tentatively identified as N-methyl-2-(methylthio) benzamide (molecular weight 182.06).

CONCLUSION The notified chemical is inherently biodegradable.

TEST FACILITY Brixham Environmental Laboratory (2008)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish – freshwater

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – Flow-through conditions

Species Rainbow trout (*Oncorhynchus mykiss*)

Exposure Period 96 hours

Auxiliary Solvent Acetone (≤0.1 mL/L)

Water Hardness 44-48 mg $CaCO_3$/L

Analytical Monitoring The concentration of the test substance was determined by HPLC/UV

Remarks – Method After range-finding tests, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 10–12°C, pH 6.4–6.8, 8.4–10 mg O_2/L. Statistical endpoints were estimated by moving binomial analysis (non-linear interpolation).

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality%*				
Nominal	*Actual*		*6h*	*24h*	*48h*	*72h*	*96h*
0	–	10	0	0	0	0	0
0.031	0.019	10	0	0	0	0	0
0.063	0.050	10	0	0	0	0	0
0.13	0.11	10	0	0	0	0	0*
0.25	0.22	10	0*	40	40*	40	40*
0.50	0.46	10	100	100	100	100	100

* Sublethal effects observed.

LC50	0.24 mg/L at 96 hours (95% CI: 0.11 to 0.46 mg/L)
NOEC	0.050 mg/L at 96 hours
Remarks – Results	Sublethal effects observed in the fish included darkened pigmentation, loss of equilibrium, lethargy or location at bottom of vessel. There was no observed mortality or adverse effects in the control or solvent control and, as there were only slight deviations from other acceptability criteria, the test is considered to be valid. The reported toxicity endpoints were based on mean measured concentrations.
CONCLUSION	The notified chemical is very toxic to freshwater fish
TEST FACILITY	Springborn Smithers Laboratories (2007a)

C.2.2. Acute toxicity to fish – seawater

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Flow-Through Conditions
Species	Sheepshead Minnow (*Cyprinodon variegatus*)
Exposure Period	96 hours
Auxiliary Solvent	Acetone (≤0.1 mL/L)
Water Salinity	20 ‰
Analytical Monitoring	The concentration of the test substance was determined by HPLC/UV
Remarks – Method	After a range-finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 21–23°C, pH 7.5–7.8, 6.1–8.8 mg O_2/L. Statistical endpoints were estimated by binomial probability.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality%*				
Nominal	*Actual*		*6h*	*24h*	*48h*	*72h*	*96h*
0	0	10	0	0	0	0	0
0. 31	0.33	10	0	0	0	0	0
0. 63	0.40	10	0	0	0	0	0
1.3	1.0	10	0	0	0	0	0
2.5	2.2	10	100	100	100	100	100
5.0	4.3	10	100	100	100	100	100

LC50	1.5 mg/L at 96 hours (95% CI: 1.0 to 2.2 mg/L)
NOEC	1.0 mg/L at 96 hours
Remarks – Results	There was no observed mortality or adverse effects in the control or solvent control and, as there were only slight deviations from other acceptability criteria, the test is considered to be reliable. There were no observed adverse effects in the fish exposed to the test substance at the lower concentrations tested (0.33, 0.40 or 1.0 mg/L). The reported toxicity endpoints were based on mean measured concentrations.
CONCLUSION	The notified chemical is toxic to marine fish
TEST FACILITY	Springborn Smithers Laboratories (2009a)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Flow-Through Conditions.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone (≤0.1 mL/L)
Water Hardness	160 mg $CaCO_3$/L
Analytical Monitoring	The concentration of the test substance was determined by HPLC/UV
Remarks – Method	After a range-finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 18–21°C, pH 7.9–8.0, 8.6–9.3 mg O_2/L. Statistical endpoints were estimated by binomial analysis (non-linear interpolation).

RESULTS

Concentration mg/L		*Number of D. magna*	*% Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	2 × 10	0	0
0.39	0.24	2 × 10	0	0
0.79	0.65	2 × 10	0	0
1.6	1.3	2 × 10	5	100
3.2	2.8	2 × 10	20	90
6.3	6.1	2 × 10	100	100

EC50	0.92 mg/L at 48 hours (95% CI: 0.65 to 1.3 mg/L)
NOEC	0.65 mg/L at 48 hours
Remarks – Results	There was no observed immobility in the control or solvent control and, as there were only slight deviations from other acceptability criteria, the test is considered to be reliable. There was no immobility observed in daphnids exposed to the test substance at the lower concentrations tested (0.24 or 0.65 mg/L). The reported toxicity endpoints were based on mean measured concentrations.
CONCLUSION	The notified chemical is very toxic to aquatic invertebrates
TEST FACILITY	Springborn Smithers Laboratories (2007b)

C.2.4. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia magna*, Reproduction test – Flow-through
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Acetone (≤0.05 mL/L)
Water Hardness	152-158 mg $CaCO_3$/L
Analytical Monitoring	The concentration of the test substance was determined by HPLC
Remarks - Method	After a preliminary test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 18.4–21.2°C, pH 7.43–7.97, 7.85–9.22 mg O_2/L. The data was checked for normality by Shapiro-Wilks' Test, homogeneity of

variance by Bartlett's Test, and the survival endpoints were determined by Kruskal-Wallis's test followed by Dunn's Multiple comparison test or bootstrap analysis. Bonferroni t-test was used to determine the statistical endpoints for growth and reproduction.

RESULTS

Day 21			
*Mean measured concentration (mg/L)**	*Mean percent adult survival*	*Mean number of offspring produced per female – cumulative*	*Mean total body length*
0†	97.5†	77†	4.38†
0.053	100	77	4.42
0.097	100	80	4.45
0.20	97	84	4.46
0.42	80	86	4.49
0.95	10	57	4.25

*Arithmetic mean; †Pooled results of dilution water control and solvent control.

EC50 (reproduction)	>0.42 mg/L at 21 days
NOEC (reproduction)	0.42 mg/L at 21 days
EC50 (survival)	0.70 mg/L at 21 days
NOEC (survival)	0.42 mg/L at 21 days
Remarks - Results	There was no mortality in the dilution water control, and other acceptability criteria were fulfilled, thereby validating the test. Statistical analysis determined a significant difference in survival among daphnids exposed to the highest concentration tested (0.95 mg/L) when compared to the pooled control, and the EC50 and NOEC for survival were determined to be 0.70 mg/L and 0.42 mg/L, respectively. Statistical analyses determined no significant reduction in offspring per female or reduction in body length in the treatment levels 0.053 to 0.42. Due to survival effects in the treatment level 0.95 mg/L, the NOEC and LOEC values for both reproduction and growth were determined to be 0.42 and >0.42 mg/L.
CONCLUSION	The notified chemical is toxic to aquatic invertebrates with long lasting effects
TEST FACILITY	Springborn Smithers Laboratories (2009b)

C.2.5. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata* (Green alga)
Exposure Period	72 hours
Concentration Range	Actual: 0.0040, 0.010, 0.026, 0.064, 0.16, 0.40 and 1.0 mg/L Measured: 0.0043, 0.011, 0.027, 0.068, 0.16, 0.42 and 1.1mg/L
Auxiliary Solvent	None
Water Hardness	0.15 mmol Ca^{2+} and Mg^{2+}
Analytical Monitoring	The concentration of the test substance was determined by HPLC/UV
Remarks - Method	After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 24°C, pH 7.1–9.6. Statistical endpoints were estimated by Williams' Test and linear regression of response methods.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
0.21	0.084	0.33	0.068
(95% CI: 0.17 to 0.25)		(95% CI: 0.32 to 0.34)	

Remarks – Results

The cell growth in the control increase from initial density by more than 16 times after 72 hours of growth, and as the other validity criteria were fulfilled, the test is thereby validated.

The reported toxicity endpoints were based on mean measured concentrations.

At test termination, an aliquot was removed from the composite 1.0 mg/L nominal solution and diluted. The cell density increased markedly, and thereby the notified chemical was indicated to have an algistatic, rather than an algicidal effect on the growth of algae.

CONCLUSION The notified chemical is very toxic to algae

TEST FACILITY Springborn Smithers Laboratories (2007c)

C.2.6. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum Activated sludge from a primarily domestic wastewater treatment plant
Exposure Period 3 hours
Concentration Range Nominal: 1.0, 3.0, 10, 33 and 100 mg/L
Remarks – Method After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to protocol were reported. Test conditions were: 19.8–19.9°C, pH 7.09–7.95. Statistical endpoints were estimated by the Strathkelvin program.

RESULTS
IC50 13.0 mg/L
NOEC Not reported
Remarks – Results The median inhibitory concentration (IC50 = 5.1 mg/L) for the reference substance, 3,5-dichlorophenol, was determined to be within the acceptable limits (5 to 30 mg/L), and other acceptability criteria were fulfilled, thereby validating this test.

CONCLUSION The notified chemical is harmful to microbial respiration

TEST FACILITY Springborn Smithers Laboratories (2009c)

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