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August 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Fatty acids, tall-oil, reaction products with bisphenol A, epichlorohydrin, glycidyl tolyl ether and triethylenetetramine

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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 conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Energy.

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

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1648	1. Huntsman Polyurethanes (Australia) Pty Ltd 2. Jotun Australia Pty Ltd 3. Rebain International (Aust) Pty Ltd	Fatty acids, tall-oil, reaction products with bisphenol A, epichlorohydrin, glycidyl tolyl ether and triethylenetetramine	Yes	≤ 40 tonnes per annum	Component of industrial coatings/paints

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Skin irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage (Category 1)	H318 – Causes serious eye damage
Skin sensitiser (Category 1)	H317 – May cause an allergic skin reaction

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute (Category 1)	H400 – Toxic to aquatic life
Chronic (Category 1)	H410 – Toxic to aquatic life with long lasting effects

Human health risk assessment
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

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

Environmental risk assessment
On the basis of the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin irritation (Category 2): H315 – Causes skin irritation
  - Serious eye damage (Category 1): H318 – Causes serious eye damage
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

  The above should be used for products/mixtures containing the notified chemical, if applicable, based on the concentration of the notified chemical present.

Health Surveillance

- As the notified chemical is a strong 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 allergic skin reaction.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Automated and enclosed systems during reformation and packaging
  - Spray booth or equivalent conditions during spray application
  - Local exhaust ventilation if formation of mist or aerosol is expected

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure to the notified chemical:
  - Avoid contact with skin or eyes
  - Avoid inhalation of aerosols or mists

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Impervious gloves
  - Coverall
  - Chemical resistant footwear
  - Face shield
  - Respiratory protection if formation of mist or aerosol is expected

  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 Code of Practice for *Spray Painting and Powder Coating* (SWA, 2015) or relevant State or Territory Code of Practice.

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

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

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Storage

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

Emergency procedures

- Spills or accidental 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 intended to be used in products available to the public;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of industrial coatings/paints, or is likely to change significantly;
  - the amount of chemical being introduced has increased, 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.

Safety Data Sheet
The SDS of products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Huntsman Polyurethanes (Australia) Pty Ltd (ABN: 40 090 446 165)
Gate 3, 765 Ballarat Road
DEER PARK VIC 3023

Jotun Australia Pty Ltd (ABN: 29 007 126 696)
9 Cawley Road
BROOKLYN VIC 3012

Rebain International (Aust) Pty Ltd (ABN: 50 102 669 536)
53 – 55 Rodeo Drive
DANDENONG SOUTH 3175

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: other names, molecular and structural formulae, molecular weight and analytical data.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: water solubility, hydrolysis as a function of pH, dissociation constant, flammability, explosive properties, oxidising properties and acute inhalation toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Europe (2017)
Canada (2017)
US (1997)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
ARADUR® 450 (product containing the notified chemical at ≤ 70% concentration)
Jotachur 1709 Comp B (product containing the notified chemical at ≤ 25% concentration)

CAS NUMBER
186321-96-0

CHEMICAL NAME
Fatty acids, tall-oil, reaction products with bisphenol A, epichlorohydrin, glycidyl tolyl ether and triethylenetetramine

MOLECULAR WEIGHT
Number average molecular weight > 500 g/mol

ANALYTICAL DATA
Reference NMR, IR, HPLC, LC-MS and GPC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
100% (UVCB substance)

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Yellow/brown liquid

Property	Value	Data Source/Justification
Melting Point	< -60 °C	Measured
Boiling Point	> 400 °C at 101.3 kPa	Measured
Density	1,010.7 kg/m^3 at 20 °C	Measured
Viscosity	> 10 Poise at ≤ 50 °C	Measured
Vapour Pressure	6.002 × 10^{-7} kPa at 20 °C	Measured
Water Solubility	Not determined	Attempts to measure the water solubility failed as no method could be validated for this UVCB substance.
Hydrolysis as a Function of pH	Not determined	No hydrolysable functionality
Partition Coefficient (n-octanol/water)	log P_{ow} = 3.38 at 25 °C	Estimated by the HPLC simulation method using isocratic (single solvent) elution
Adsorption/Desorption	log K_{oc} = 2.37	Expected to partition to surfaces from water in the environment based on its surfactant properties and cationic functionalities
Dissociation Constant	Not determined	Contains potential cationic moieties and expected to be ionised in the environmental pH range (4 – 9)
Flash Point	> 110 °C at 97.867 kPa	Measured
Flammability	Not determined	Not expected to be a flammable liquid based on flash point
Autoignition Temperature	Not determined	Not expected to autoignite under normal conditions of use
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties
Stability Testing	Stable under the conditions of vapour pressure testing	Measured

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical (at ≤ 70% concentration) will be imported in the product ARADUR® 450. The product ARADUR® 450 will be reformulated and repackaged into finished two-component industrial coating/paint products in Australia.

The notified chemical will also be imported in the product Jotachur 1709 Comp B (at ≤ 25% concentration), which is one component of a ready-to-use two-component industrial coating/paint product. The ready-to-use product will be distributed to industrial end-users without further reformulation or repackaging.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	2	10	20	30	40

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
Huntsman Polyurethanes (Australia) Pty Ltd
Jotun Australia Pty Ltd
Rebain International (Aust) Pty Ltd

TRANSPORTATION AND PACKAGING
The product containing the notified chemical will be imported in 20 L or 200 kg steel drums to be distributed to industrial customers by road for reformulation.

Reformulated or imported finished industrial coating/paint products containing the notified chemical will be stored and transported in 1 – 25 kg steel cans or drums by road.

USE
The notified chemical will be used as a curing agent in two-component industrial coating/paint systems. Coating/paint products containing the notified chemical will be used by industrial and professional users for applications to concrete or metal surfaces.

OPERATION DESCRIPTION
Manufacture of the notified chemical will not occur in Australia.

Reformulation/repackaging
At reformulation sites, factory operators will be involved in transferring the product containing the notified chemical from imported containers into open stainless-steel blending tanks under local exhaust ventilation. The transfer operation will involve manual measuring and pouring. Paint agitator equipment will be used to blend the components of the coating/paint. During mixing, the tanks will be in an enclosed environment.

Quality assurance (QA) personnel will take samples and test the final coating/paint formulations containing the notified chemical. Samples will be taken by dipping containers into the mixer and transferred into clean, sealed steel containers for further examinations in laboratory.

Filling line staff will operate and clean the automated filling equipment. The finished industrial coating/paint products containing the notified chemical (at ≤ 25% concentration) will be filled into 1 – 25 kg cans or drums by gravity feed. Filling lines will be equipped with ventilation extraction systems.

Finished coating/paint products will be stored in warehouses and further distributed to end users.

End-use operations
The two-part industrial coating/paint system (containing the notified chemical at ≤ 25% concentration) will be applied using specialised spray painting equipment, where the two parts of the coating/paint will be mixed in-line at the application nozzle before the coating/paint is sprayed onto a surface. The spray equipment is designed to mix and dispense the two-part coating/paint system at the correct ratio, temperature and pressure.

In a typical use scenario, professional users will manually pour the coating/paint products containing the notified chemical into the spray equipment. Spray painting applications will be performed in spray booths fitted with ventilation and directional airflow (down draft) to capture and filter any mists and overspray. After the spray operation is completed, the equipment will be cleaned using enclosed cabinets. A suitable solvent will be forced through the equipment under pressure whilst the trigger unit will be maintained in an open position. A clean cloth dampened with an appropriate solvent will be used to remove coating/paint drips and splashes from exterior surfaces. Wastes will be collected for disposal.

Final coating/paint products containing the notified chemical (≤ 25% concentration) can also be applied by brush and roller. Equipment used for applying coating/paint products can be cleaned using a cloth or newspaper to remove the majority of the residues and then rinsed with water.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	0	0
Workers	2	20
Blending/formulation	8	20
Professional tradesmen	8	20

EXPOSURE DETAILS

Transport and Storage
Transport and storage workers are not expected to be exposed to the notified chemical except in the unlikely event of an accident as the products containing the notified chemical will be sealed in containers during the transport and storage operations.

Reformulation
During reformulation operations, dermal and ocular exposure of workers to the notified chemical at ≤ 70% concentration may be possible when weighing and transferring of the product containing notified chemical from imported containers into blending tanks. The loading operation will be carried out under a fume extractor and blending will occur in a closed mixing tank under local exhaust ventilation. Inhalation of the notified chemical is not expected unless the chemical becomes airborne. The notifier stated that personal protective equipment (PPE), such as coveralls, gloves, suitable respirators, and eye protection, will be used when carrying out the activities.

During filling operations, potential exposure of workers to the notified chemical in finished industrial coating/paint products (at ≤ 25% concentration) will also likely be through dermal or ocular routes. The exposure is expected to be minimal due to the use of automated/enclosed systems and appropriate PPE.

Members of QA staff will wear laboratory coats, gloves and safety glasses to minimise exposure to the notified chemical in the samples during testing.

End Use
The industrial coating/paint products containing the notified chemical will be used for applications to concrete or metal surfaces by industrial and professional users. Dermal and ocular exposure of workers to the notified chemical at ≤ 25% concentration may occur when opening cans of the coatings/paints and manually pouring the contents into spray equipment. In addition, exposure may occur during connecting and disconnecting transfer hoses. If leakages happen during applications, workers may also be potentially exposed to the notified chemical at ≤ 25% concentration mainly via dermal and ocular routes.

Workers may be exposed to the notified chemical at ≤ 25% concentration by inhalation of the aerosolised coatings/paints during spray applications. Inhalation is expected to be minimal as the coatings/paints will be applied in spray booths and workers are expected to use appropriate PPE, including full-face self-contained breathing apparatuses, disposable overalls, impervious gloves and safety boots.

Dermal, ocular and inhalation exposure to the notified chemical at ≤ 25% concentration may also occur during the cleaning of the spray equipment. This operation will take place within enclosed cabinets and operators are expected to wear appropriate PPE including overalls, safety glasses or goggles, impervious gloves and respirators during the cleaning procedure.

6.1.2. Public Exposure
The products containing the notified chemical will only be used by industrial and professional users. It will not be sold to the public for do-it-yourself (DIY) use.

Members of the public may come into contact with articles coated with the finished industrial coating/paint products containing the notified chemical. However, once dried the notified chemical is expected to be bound into the inert matrix of the coating/paint and will not be available for further exposure.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Skin corrosion – *in vitro* human skin model test (EpiDerm™)	non-corrosive
Skin irritation – *in vitro* human skin model test (EpiDerm™ SIT EPI-200)	irritating
Eye irritation – *in vitro* bovine corneal opacity and permeability (BCOP) Test	no prediction could be made
Rabbit, eye irritation	corrosive
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation (EC_3 < 0.1%)
Rat, repeat dose oral toxicity – 90 days	NOAEL = 100 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation tests	non genotoxic
Genotoxicity – *in vitro* chromosome aberration test in human lymphocytes	non genotoxic
Rat, combined repeated dose oral toxicity study with the reproduction/developmental toxicity screening test*	NOAEL = 1,000 mg/kg bw/day

* Study on an analogue chemical

Toxicokinetics, metabolism and distribution

No toxicokinetic data on the notified chemical were submitted. Given the notified chemical is a UVCB with low molecular weight (< 500 g/mol) chemical constituents and has a log P_{ow} of 3.38, absorption across biological membranes may occur.

Acute toxicity

Based on the study reports submitted, the notified chemical is of low acute toxicity via the oral and dermal routes of exposure in rats (LD50 > 2,000 mg/kg bw).

No acute inhalation toxicity data were submitted for the notified chemical. If aerosolised, the notified chemical may be irritating to the respiratory tract based on the irritation properties observed in skin and eye irritation studies.

Irritation

Based on an *in vitro* skin corrosion/irritation test conducted, the notified chemical was considered to be non-corrosive but irritating to the skin. The notified chemical meets the criteria for classification as a skin irritant (Category 2) according to the GHS.

In an *in vitro* bovine corneal opacity and permeability (BCOP) test, the *in vitro* irritancy score (IVIS) for the notified chemical was 11.73 and no prediction of eye irritation properties of the notified chemical could be made.

Following the BCOP test, an *in vivo* eye irritation study was conducted on a rabbit. Scattered or diffuse areas of cornea opacity and iridial inflammation were noted during testing. In addition, moderate or severe conjunctival irritation was noted in the test animal, persisting for 72 hours after instillation. Maximal conjunctival inflammation (swelling grade 4) was noted 24 hours after instillation and was associated with redness (grade 3) at 48 hours after instillation. As there was no evidence of recovery by 72 hour observation, the animal was euthanised after the observation. The test substance meets the criteria for classification as causing serious eye damage (Category 1) according to the GHS. The notified chemical causes irreversible effects on the eye.

Sensitisation

In a mouse local lymph node assay (LLNA), the notified chemical up to 50% concentration showed clear evidence of strong/extreme skin sensitisation. The notified chemical meets the criteria for classification as a strong skin sensitiser (Category 1) according to the GHS.

Repeated dose toxicity
In a 90-Day repeated dose oral toxicity study in rats, the notified chemical was administered at dose levels of 100, 300 and 1,000 mg/kg bw/day. Three unscheduled deaths occurred during the study in the high dose group. The high dose level was reduced to 600 mg/kg bw/day on Day 12 – 13 and then further reduced to 450 mg/kg bw/day on Day 21 – 20. No further unscheduled deaths occurred at the 450 mg/kg bw/day dose.

Clinical signs for the animals in the high dose group, included episodes of increased post-dosing salivation and noisy respiration for both sexes. The incidence was higher before the dose was reduced. Sporadic instances of hunched posture, decreased respiration rate, laboured respiration, and diarrhoea were also observed occasionally in the surviving animals during the study.

For males in the mid and high dose groups, increases in liver enzymes (mean aspartate aminotransferase and alanine aminotransferase activities) were observed. These increases were associated with higher liver weights for males in the high dose group; however, there was no associated histopathological changes reported at microscopic evaluation. The findings were not considered by the study authors to represent an adverse effect. Additionally, similar increased liver weights were observed for females in the mid and high does groups without any corresponding increase in liver enzymes.

For males in the mid and high dose groups, increase in mean adrenal weights and decrease in mean kidney weights were observed. For females in the mid and high dose groups, increased mean kidney weights were observed. There were no macroscopic findings at necropsy.

Histopathological changes detected at microscopic evaluation of the tissues, which were considered to be related to treatment, were restricted to the mesenteric lymph node. At all dosages, minimal to mild histiocytosis, mainly evident as histiocyte aggregates in the sinusoids, was observed in both sexes. Males in the high dose group, showed an increase in generation, distribution and then cellular destruction of red blood cells (erythrocytosis and erythrophagocytosis). Combination of histiocytosis with erythrocytosis and erythrophagocytosis was considered a potential adverse effect by the study authors.

A No Observed Adverse Effect Level (NOAEL) was established by the study authors as 100 mg/kg bw/day for the notified chemical based on male body weight effects observed at higher doses.

Reproduction and developmental toxicity
No reproduction and developmental toxicity study was provided for the notified chemical. A combined repeated dose toxicity study with the reproduction and developmental toxicity screening test in rats on an analogue chemical (precursor of the notified chemical) was submitted. It is noted that the analogue chemical does not contain bisphenol A and several other reactants, which are included in the notified chemical.

The analogue chemical was administered to rats for a period of 42 days consecutively at dose levels of 100, 300 and 1,000 mg/kg bw/day. A female, in the high dose group was euthanised on Day 1 due to severe clinical signs, but it was considered an isolated incident.

The results of the study indicated the possibility of a slight sex difference in response to the analogue treatment. Males in the high dose group were characterised by statistically significant reductions in mean body weight gain. Lower mean heart weights in the males in this dose group were also observed with no mortalities and changes in pathology. These changes were not seen in the female rats and therefore not considered by the study authors to be adverse.

For females in the high dose group, a statistically significant reduction in mean body weight gain during the last week of gestation was observed, however, lactation, pup body weight and pup survival were unaffected.

There was no effect of the analogue chemical on mating, fertility or fecundity indices. The majority of animals mated within one oestrous cycle. There was no adverse effect of treatment on gestational length, number of implantation sites or pups born, pup survival or pup body weight gain. No remarkable necropsy findings on pups were noted.

A NOAEL for the analogue chemical was established by the study authors as 1,000 mg/kg bw/day, based on the highest dose tested.

Mutagenicity/Genotoxicity
The notified chemical was found to be non mutagenic in a bacterial reverse mutation assay and in an *in vitro* mammalian cell gene mutation test using mouse lymphoma cells. The notified chemical was also determined to be non clastogenic in an *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Skin irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage (Category 1)	H318 – Causes serious eye damage
Skin sensitiser (Category 1)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation
Based on the toxicological information submitted, the notified chemical is a strong skin sensitiser that may cause allergic skin reactions. The notified chemical is also considered to cause serious eye damage and skin irritation.

The notified chemical contains phenol, 4,4'-(1-methylethylidene) bis- (CAS No. 80-05-7), also known as bisphenol A, as a reactant in the manufacture of the notified chemical. Although bisphenol A is listed by Safe Work Australia in the *Hazardous Chemical Information System (HCIS)* as a reproductive toxicant (Category 2), it will be present in the notified chemical as polymerised form, bound into inert matrix of cured coatings/paints and will not be available for exposure after curing. However, slow release of bisphenol A or derivatives in trace amounts may be possible over time from polymer degradation under certain conditions, such as exposure to intense UV light or temperature > 350 °C. It is expected that the release of bisphenol A from polymer degradation is unlikely to reach a biologically significant level to cause adverse health effects.

6.3.1. Occupational Health and Safety

Reformulation
Reformulation workers may come into contact with the notified chemical at ≤ 70% concentration. Main routes are expected to be dermal and accidental ocular exposure is also possible. Serious eye damage, skin sensitisation and irritation effects are possible if workers are exposed to the notified chemical. Safe work practices, use of engineering controls and PPE, including impervious gloves, protective clothing and eye protection, would reduce the risk of adverse health effects. Inhalation exposure during reformulation is unlikely to occur due to the low vapour pressure of the notified chemical and the use of automated/enclosed systems.

End-use
Throughout end-use workers may be exposed to the notified chemical at ≤ 25% concentration when handling products containing the notified chemical and during spray applications. Workers may also be potentially exposed to the notified chemical at ≤ 25% concentration if leakages occur. Systemic absorption of the notified chemical through dermal exposure is possible due to the presence of low molecular weight chemical constituents. The likely exposure routes are inhalation, dermal and ocular, with the potential for serious eye damage, skin sensitisation and irritation effects to workers. The use of safe work practices, engineering controls and appropriate PPE including protective clothing, impervious gloves and safety glasses, is expected to mitigate the risk of potential adverse health effects to workers from use of the notified chemical.

The inhalation toxicity for the notified chemical has not been fully determined. However, the proposed use of engineering controls including spray booths, general exhaust ventilation and appropriate PPE including respirators, will reduce the potential for exposure during the operations, and reduce the risk of possible adverse effects.

Provided that the work place controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

6.3.2. Public Health

Products containing the notified chemical will only be used by workers in areas that will not be accessible to the general public. Members of the public may come into contact with articles coated with products containing the notified chemical. However, the notified chemical is expected to be cured and cross-linked to form an inert matrix and will not be available for further exposure.

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

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The release of the notified chemical to the environment during importation, storage, and transport is unlikely. Release during reformulation in Australia is expected to arise from spills, formulation equipment cleaning and residues in import containers. Accidental spills during transport or reformulation are expected to be captured in a solvent. The solvent is recycled with residue being disposed of to landfill. Import containers will either be recycled or disposed of through an approved waste management facility. Less than 2% of the import volume is estimated to be released to landfill as a result of reformulation in Australia.

RELEASE OF CHEMICAL FROM USE

During application by spray, it is expected that up to 20 – 30% of the notified chemical will be released as overspray, which will be collected and disposed of to landfill. Residues containing the notified chemical on brushes and rollers are expected to be rinsed into containers and then allowed to cure before disposal as solid wastes to landfill. Less than 2% of the notified chemical may remain as residues in product containers and these will be disposed of to landfill or recycled. Equipment used to apply the coating formulations may be rinsed with solvent. The solvent is expected to be recycled with residue being disposed of to landfill. It is estimated that less than 1% of the import volume of the notified chemical will be collected from cleaning of equipment, which is expected to be treated and disposed of by a licensed waste contractor.

RELEASE OF CHEMICAL FROM DISPOSAL

The majority of the notified chemical will be cured into an inert matrix with other chemical substances as part of the coating process and hence will be immobilised within a film on coated articles. The articles coated with products containing the notified chemical, at the end of their useful life, are expected to either go to metal recyclers or be disposed of to landfill.

7.1.2. Environmental Fate

The notified chemical was determined not to be readily biodegradable (9% biodegradability over 28 days). For the details of the environmental fate study, please refer to Appendix C.

When used as one component of a two-part system for industrial coating of steel, the majority of the notified chemical is expected to cross-link to form an inert polymer film after its application. The notified chemical will share the fate of the coated articles, which are expected to be eventually disposed of to landfill or be subjected to metal reclamation. In its cured form, the notified chemical is not expected to be bioavailable or mobile in the environment. The notified chemical will eventually degrade in landfill via biotic or abiotic pathways, or by thermal decomposition during metal reclamation processes, to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The notified chemical is not expected to be present at significant concentrations in the aquatic environment because of the very low potential for direct release to surface waters when used on concrete or metal surfaces for industrial applications. A Predicted Environmental Concentration (PEC) has therefore not been calculated.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LL50 (96 h) = 1.8 (WAF)*	Toxic to fish
Daphnia Toxicity	EL50 (48 h) = 0.7 (WAF)*	Very toxic to aquatic invertebrates
Algal Toxicity	E_rL50 (72 h) = 0.186 (WAF)* NOEL (72 h) = 0.032	Very toxic to algae
Inhibition of Bacterial Respiration	EC50 (3 h) = 157.6 mg/L (loading)	Not inhibitory to bacterial respiration
Other	LC50 (28 days) > 1,000 mg/kg	Not toxic to earthworms

WAF*= Water Accommodated Fraction

Based on the endpoints for fish, Daphnia and algal toxicity, the notified chemical is considered to be very toxic to aquatic organisms on an acute basis, under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) (United Nations, 2009). Therefore, the notified chemical is formally classified as "Acute Category 1; Toxic to aquatic life" under the GHS. Based on the acute toxicity and potential for the notified chemical to persist in the environment, the chronic hazard of the notified chemical has been formally classified as "Chronic Category 1; Toxic to aquatic life with long lasting effects" under the GHS.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint of the most sensitive species (Daphnia, 48 hours EL50 = 0.7 mg/L). An assessment factor of 100 has been used, as acute toxicity endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EL50 (Daphnia)	0.7	mg/L
Assessment Factor	100	
PNEC:	7	µg/L

7.3. Environmental Risk Assessment

A Risk Quotient is unable to be quantified, as a PEC was not calculated. There is no significant aquatic release of the notified chemical anticipated based on its reported use pattern. Moreover, after curing, the majority of the notified chemical will be irreversibly incorporated into an inert matrix and it is not expected to be mobile, bioavailable or bioaccumulative. Uncured notified chemical waste is not expected to bioaccumulate in biota based on the notified chemical's surface activity. On the basis of the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point < -60 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined by differential scanning calorimetry (DSC)
Test Facility	Smithers (2013a)

Boiling Point > 400 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Determined by differential scanning calorimetry (DSC)
Test Facility	Smithers (2013a)

Density 1,010.7 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Determined using gas comparison pycnometer
Test Facility	Smithers (2013a)

Viscosity > 10 Poise at ≤ 50 °C

Method	OECD TG 114 Viscosity of Liquids
Remarks	Determined using a REL cone and plate viscometer
Test Facility	Smithers (2013a)

Vapour Pressure 6.002×10^{-7} kPa at 20 °C (using weight average molecular weight)
7.346×10^{-7} kPa at 20 °C (using number average molecular weight)

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Determined using a vapour pressure measuring device with Knudsen cell
Test Facility	Smithers (2013a)

Partition Coefficient (n-octanol/water) log P_{ow} = 3.38 at 25 °C (as weighted average)

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Partition coefficient was estimated by the HPLC simulation method using isocratic elution. The test substance eluted as multiple components. As a definitive value for the partition coefficient was not determined, the 95% confidence range could not be estimated. The partition coefficient was calculated using the weighted average of components eluted.
Test Facility	Smithers (2013a)

Flash Point > 110 °C at 97.867 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	A closed cup flash point tester was used
Test Facility	Smithers (2013a)

Stability Testing Stable under the conditions of vapour pressure testing

Method	IR spectra comparison
Remarks	IR spectra of the test substance before, during and after vapour pressure testing and a separate untested stability sample were compared.

The intensity of each peak had minor differences but the wave numbers were unchanged after testing. Therefore, it was concluded that the notified chemical was stable for the duration of the test.

Test Facility Smithers (2013a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Toxicity – Oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/HsdHan:WIST
Vehicle	Polyethylene glycol (PEG) 400
Remarks - Method	No major deviations from the test guideline were reported.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 F	2,000	0/3
2	3 F	2,000	0/3

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted in the animals treated at 2,000 mg/kg bw.
Effects in Organs	No abnormities were observed at necropsy
Remarks - Results	All animals showed expected body weight gain during the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Covance (2013a)

B.2. Acute Toxicity – Dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/HsdHan:WIST
Vehicle	None
Type of dressing	Semi-occlusive
Remarks - Method	The test substance was used as supplied. No major deviations from the test guideline were reported.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	2 (1 M/1 F)	2,000	0/2
2	10 (5 M/5 F)	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No evidence of dermal oedema was observed. Very slight to well-defined erythema was noted in all male animals on Day 2 of application. Very slight erythema persisted in 1 male till Day 5 – 6 after application, and in another male till the end of the study. Very slight erythema was noted in all female animals on Day 2 and Day 5 – 7 of application. Very slight erythema was noted in 1 female animal on Day 3 – 4. Very slight erythema persisted in 5 female animals

	till Day 14 – 15. Other dermal reactions noted in the test animals were brown discolouration of the skin, scabbing and shiny skin. The brown discolouration of the skin was considered by the study authors to be due to partial corrosion. The scabbing was considered to be the result of drying of slight tissue exudate from sores induced at the application site.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed
Effects in Organs	Abnormalities noted at necropsy were confined to the appearance of sores at the treatment site.
Remarks - Results	No clinical signs were observed due to treatment. All animals had expected body weight gain during the observation period, except for 1 female that showed no change in body weight during the first week and another female that showed a slight loss in body weight during the second week.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route however is a skin irritant.
TEST FACILITY	Covance (2013b)

B.3. Irritation – Skin (*in vitro* EpiDerm™ Reconstituted Human Epidermis Model)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 *In vitro* Skin Corrosion – Human Skin Model Test OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method EC Council Regulation No 440/2008 B.40 BIS. *In vitro* Skin Corrosion – Human Skin Model Test EC Council Regulation No 440/2008 B.46. *In vitro* Skin Irritation – Reconstructed Human Epidermis Model Test (2009)
Vehicle	None
Remarks - Method	Due to the viscosity of the test substance, it was not possible to accurately weigh the required 25 mg of test substance for each procedure. The test substance with container and culture loop were weighed before and after the application to the whole tissue surface and the difference was used to calculate the total weight of test substance applied. This deviation was considered by the study authors not to have affected the integrity of the study. Skin corrosion test (SCT): The EpiDerm™ test system was used. Test substance was used as supplied. The positive control used was potassium hydroxide (8 N) and the negative control was sterile distilled water. Skin irritation test (SIT): The EpiDerm™ SIT (EPI-200) test system was used. Test substance was used as supplied. The positive control was sodium dodecyl sulfate (SDS) at a concentration of 5% and the negative control was phosphate buffered saline (PBS). The test substance was found to be able to directly reduce 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT). Therefore, an additional procedure using freeze-killed tissues was performed. Assessment of MTT interacting substances was performed in accordance with the method for SCT, but not for SIT. No other major deviations from the test guideline were reported.

RESULTS

SCT – exposure of 3 minutes

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*
Negative Control	1.582	100
Test Substance		
Fresh Tissue	1.052	–
Freeze Killed Tissue#	0.180	–
*Corrected**	0.872	55
Positive Control	0.281	18

OD = optical density
# Indicative of non-specific reduction of MTT by the test substance
* Corrected for non-specific reduction of MTT and used for relative viability calculation

SCT – exposure of 60 minutes

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*
Negative Control	1.605	100
Test Substance		
Fresh Tissue	0.861	–
Freeze Killed Tissue#	0.217	–
*Corrected**	0.644	41
Positive Control	0.127	8

OD = optical density
# Indicative of non-specific reduction of MTT by the test substance
* Corrected for non-specific reduction of MTT and used for relative viability calculation

SIT

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative Control	2.098	100	15.298
Test Substance	0.152	7.2	0.844
Positive Control	0.103	4.9	0.490

OD = optical density; SD = standard deviation

Remarks - Results

The test substance was deemed to interact with MTT. Therefore, freeze killed issues were used as controls to correct non-specific reduction of MTT by the test substance.

The acceptance criteria for both the negative and positive controls were satisfied, and the variation between replicates was satisfactory.

SCT: As the mean viability was 55% and 41% following 3 minute and 60 minute exposures, respectively, the test substance was not corrosive according to the test guidelines.

SIT: As the relative mean viability of tissues exposed to the test substance was < 50%, test substance meets the criteria for classification as a skin irritant (GHS Category 2) according to the test guidelines.

CONCLUSION

The notified chemical was irritating to the skin under the conditions of the test.

TEST FACILITY

Covance (2013c)

B.4. Irritation – Eye [*in vitro* Bovine Corneal Opacity and Permeability (BCOP) Test]

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals

	Not Requiring Classification for Eye Irritation or Serious Eye Damage
Vehicle	None
Remarks - Method	The positive control was dimethyl formamide and the negative control was sodium chloride solution at 0.9% concentration. Test substance was used as supplied. No major deviations from the test guideline were reported.

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues*	*Mean Permeabilities of Triplicate Tissues*	*IVIS*
Negative Control	0	0	0
*Test Substance**	8.3	0.226	11.73
*Positive Control**	75.7	0.595	84.58

IVIS = *in vitro* irritancy score
* Corrected for background values

Remarks - Results	The acceptance criteria for the negative and positive controls were satisfied. The corneas treated with the test substance were slightly opaque post-treatment and incubation. The corneas treated with the negative control were clear, and those treated with the positive control were cloudy and blistered. The IVIS for the test substance was determined to be 11.73.
CONCLUSION	Based on the IVIS, no prediction could be made for the notified chemical under the conditions of the test.
TEST FACILITY	Covance (2013d)

B.5. Irritation – Eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation)
Species/Strain	Rabbit/New Zealand White (HsdIf:NZW)
Number of Animals	1
Observation Period	3 days
Remarks - Method	This test followed the above BCOP test to determine the eye irritation properties of the test substance. Test substance was used as supplied. No major deviations from the test guideline were reported.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	2.67	3	> 72 h	3
Conjunctiva: chemosis	4	4	> 72 h	4
Conjunctiva: discharge	2	2	> 72 h	2
Corneal opacity	2	2	> 72 h	2
Iridial inflammation	1	1	> 72 h	1

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

Remarks - Results	Scattered or diffuse areas of cornea opacity were noted 4 hours after instillation. Discernible translucent areas of corneal opacity were noted 24 – 72 hours after treatment. Iridial inflammation was noted at all time points from 30 minutes to 72 hours after instillation. Moderate conjunctival irritation was noted 30 minutes, 1, 4 and 24 hours after instillation with severe conjunctival irritation noted 24, 48 and 72 hours after instillation. Maximal conjunctival inflammation (swelling grade 4) was noted 24 hours after instillation and was associated with redness (grade 3) at 48 hours after instillation. As there was no evidence of recovery by 72 hour observation, the animal was euthanised after the observation. The study authors concluded that the test substance meets the criteria for classification as causing serious eye damage (Category 1) according to the GHS.
CONCLUSION	The notified chemical causes irreversible effects on the eye.
TEST FACILITY	Covance (2013d)

B.6. Skin Sensitisation – Mouse Local Lymph Node Assay (LLNA)

TEST SUBSTANCE	Notified chemical
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/CaCrl
Vehicle	Acetone/olive oil 4:1
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method	No major deviations from the test guideline were reported.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4 F	2,538	–
10	4 F	29,668	11.7
25	4 F	33,609	13.3
50	4 F	32,310	12.7

EC3	< 0.1% (estimated using SI derived from 10% and 25% test concentrations)
Remarks - Results	In a preliminary screening test, one animal was treated with test substance at a concentration of 50% (w/v) in the vehicle. No signs of systemic toxicity or excessive irritation were observed. Based on the preliminary results the test substance was administered at 10%, 25% and 50% (w/v) in the vehicle for the main test. In the main test, no clinical signs indicative of systemic toxicity were noted. The vehicle and test formulation application sites remained free of irritation. Greasy fur was noted in all animals from Day 1.

	The study authors concluded that the test substance meets the criteria for classification as a skin sensitiser (Category 1) according to the GHS.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Covance (2013e)

B.7. Repeat Dose Toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents
Species/Strain	Rat/Wistar (RccHan™:WIST)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Polyethylene glycol (PEG) 400
Remarks - Method	Due to a technical error, motor activity values for 1 female animal on Day 84 were not recorded. The animal was reassessed on Day 91 and the data recorded were used for the assessment. Data collected for this animal was consistent with other animals in the study. On Day 19, 1 hour post-dosing observation was performed approximately 1 hour late. No other major deviations from the test guideline were reported.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	20 (10 M/10 F)	0	0/10
Low dose	20 (10 M/10 F)	100	0/10
Mid dose	20 (10 M/10 F)	300	0/10
High dose	20 (10 M/10 F)	1,000/600/450*	3/10

* The high dose was reduced from 1,000 mg/kg bw/day to 600 mg/kg bw/day on Day 12 – 13 of dosing, because of moribund animals. The dose was further reduced to 450 mg/kg bw/day on Day 21 – 20 of dosing due to poor body weight gain and death of one animal during week 3.

Mortality and Time to Death

One male and one female in the high dose group were euthanised on Day 20 due to a decline in clinical conditions. Gaseous distension was apparent for the gastrointestinal tract of both animals at necropsy. The male also showed pale lungs while the female showed a dark liver.

Another male in the high dose group was euthanised on Day 71 after showing notable body weight loss. Necropsy findings showed gaseous distension of the caecum.

All 3 animals displayed noisy and decreased respiration, and increased salivation before euthanasia. Hunched posture was observed in 2 of the 3 animals.

All other animals survived until scheduled necropsy.

Clinical Observations

Clinical signs for surviving animals in the high dose group, included episodes of increased post-dosing salivation and noisy respiration for both sexes, with the incidence tending to be higher when animals were receiving a dosage of 1,000 mg/kg bw/day. Sporadic instances of hunched posture, decreased respiration rate, laboured respiration, and diarrhoea were observed occasionally for 4 animals in the high dose group. The study authors considered the noisy respiration may be due to potential irritant effect to the test substance in combination with slight aspiration of the test substance formulation during the dosing procedure. However,

microscopic findings did not indicate any notable irritant effect.

Clinical signs at lower dosages consisted of episodes of noisy respiration for 2 females in the low dose group, and 7 males and 5 females in the mid dose group. Increased post-dosing salivation for 1 male and 4 females in the low dose group and in all animals in the mid dose group were also observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Assessment of blood chemistry parameters revealed higher mean aspartate aminotransferase and alanine aminotransferase activities for males in the mid and high dose groups compared with controls. These increases were associated with higher liver weights for males in the high dose group; however, there were no histopathological changes at microscopic evaluation. Increased liver weights were observed for females in the mid and high does groups without any corresponding increase in aspartate aminotransferase and alanine aminotransferase activities.

At all dosages, mean total protein levels for males were lower than the control; however, no dose response was evident. Albumin/globulin ratios were statistically significantly higher in the mid and high dose groups compared with control animals. The study authors concluded that at the treatment levels observed the high albumin/globulin ratios did not represent an adverse effect.

Effects in Organs

Macroscopic findings at necropsy did not indicate effects in animals at all doses. Statistically significant differences from control were noted for a number of organ weights; however, there were no microscopic changes. For males in the high dose group, lower absolute mean liver weights, were reported. For females in the mid and high dose groups, higher absolute mean liver weights were observed but no dose response relationship was evident.

For females in the mid and high dose groups, higher absolute and body weight relative mean kidney weights were observed without histopathological changes. Males in the mid dose group had low absolute and body weight relative mean kidney weights, but this finding was reported as to reflect the higher control values rather than due to the treatment.

Histopathological changes detected at microscopic evaluation of the tissues that were considered to be related to the treatment included findings for the mesenteric lymph node. At all doses, histiocytosis, mainly evident as histiocyte aggregates in the sinusoids, was observed in both sexes, generally at a minimal or mild severity. It was reported this change is known to occur in response to the oral administration. Males in the high dose group had erythrocytosis/erythrophagocytosis in combination with the histiocytosis.

Males in the high dose group showed lower body weight gain and lower food consumption despite the lowering of the dosage to 600 mg/kg bw/day. Females in the high dose group had no marked effects on body weight gain and food consumption.

Remarks – Results

The study authors concluded the No Observed Adverse Effect Level (NOAEL) to be 100 mg/kg bw/day. Above this dosage, treated males showed statistically significantly lower body weight gain associated with lower food intake. The body weight effects might be related to the severe irritation effects of the test substance to the gastrointestinal tract.

The study authors reported that the NOAEL was driven by male toxicity rather than effects in females. The NOAEL for the females was reported as ≥ 300 mg/kg bw/day.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 100 mg/kg bw/day by the study authors.

TEST FACILITY Envigo (2017)

B.8. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

TEST SUBSTANCE Analogue chemical

METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species/Strain	Rat/Crl:WI(Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: ≥ 42 days Dose regimen: 7 days per week Post-exposure observation period: 0.5 – 4 hours
Vehicle	Corn oil
Remarks - Method	The test substance was administered orally by gavage. Dose formulation analysis was not determined; however, dose preparation records showed that the formulations were accurately prepared. In a dose range finding study, daily oral (gavage) administration of the test substance at 100, 300 and 1,000 mg/kg bw/day was generally well tolerated, with no remarkable clinical signs. Based on these findings, dose levels of 100, 300 and 1,000 mg/kg bw/day were selected for the main study. Males were dosed once daily for 2 weeks prior to pairing, during the pairing period and for a further 2 weeks before necropsy – a minimum of 6 weeks. Females were dosed for 2 weeks prior to pairing, during pairing and until Day 4 post-partum – a total of approximately 7 weeks. The females were allowed to litter and rear their offspring to Day 4 post-partum.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	20 (10 M/10 F)	0	0/20
Low dose	20 (10 M/10 F)	100	0/20
Mid dose	20 (10 M/10 F)	300	0/20
High dose	20 (10 M/10 F)	1,000	1/20

Mortality and Time to Death

One unscheduled death was noted. A female, in the high dose group was euthanised on Day 1 post-partum due to the severity of clinical signs. This was considered by the study authors to be an isolated incident and not related to the treatment. No clinical or similar macroscopic findings at necropsy for other animals were observed.

All other animals survived until scheduled necropsy.

Clinical Observations

Noisy respiration was observed in males and females in mid and high dose groups on several occasions during the dosing period, and was not considered by the study authors to be a direct clinical effect of the treatment. Mouth rubbing, salivation and/or paddling of the forelimbs were noted in animals from immediately post-dose until the end of the day on occasions. The number of animals affected and the duration of the reactions were dose-related. These findings were considered by the study authors to be a reaction to the taste of the test substance and of no toxicological significance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

For males in the mid and high dose groups and females in the high dose group, statistically significant increases in aspartate aminotransferase and alanine aminotransferase levels were noted, indicative of liver damage. In the absence of supporting microscopic changes, these increases were not considered by the study authors to be adverse.

There were also slight increases in inorganic phosphate, urea and total cholesterol levels in females in the high dose group. In the absence of correlated organ changes, these findings were not considered by the study authors to be adverse.

There was a statistically significant reduction in mean urine volume and increase in specific gravity in males in

the high dose group. As this is only a single measurement with no visual observations of lower water consumption for these animals, this finding was considered by the study authors to be incidental.

Effects in Organs

In males in the high dose group, there was a statistically significant decrease in mean heart weight. There were no histopathological or functional changes in these males and there were no statistically significant changes in the female heart weight.

In the mesenteric lymph node, increased histiocyte foci were present in all males and most females treated at 1,000 mg/kg bw/day. The increased histiocyte foci in the mesenteric lymph node might possibly be related to the large molecular size of the test substance.

Remarks – Results

Oral gavage administration of 1,000 mg/kg bw/day of the test substance indicated the possibility of a slight sex difference in response. Administration to males in the high dose group was characterised by statistically significant reductions in mean body weight gain. Lower mean heart weights in the males in this dose group were also observed with no mortalities and no changes in pathology or reduced activity during the functional observation. These changes were not seen in female rats and were not considered by the study authors to be adverse.

For females in the high dose group, a statistically significant reduction in mean body weight gain during the last week of gestation was observed, however, lactation, pup body weight and survival was unaffected.

There was no effect of test substance on mating, fertility or fecundity indices; the majority of animals mated within one oestrous cycle. There were no adverse effects on gestational length, number of implantation sites or pups born, pup survival or pup body weight gain. No remarkable necropsy findings on pups were noted.

CONCLUSION

The NOAEL was established as 1,000 mg/kg bw/day in this study, for both systemic toxicity and reproductive and developmental toxicity in rats.

TEST FACILITY	Covance (2013f)

B.9. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure/Pre incubation procedure
Species/Strain	*Salmonella typhimurium*: TA98, TA100, TA102, TA1535 and TA1537
Metabolic Activation System	Aroclor 1254 induced rat liver S9 mix
Concentration Range in Main Test	a) With metabolic activation: 5 – 5,000 µg/plate b) Without metabolic activation: 5 – 5,000 µg/plate Due to cytotoxicity in Experiment 2, the maximum test concentration for most of the strains was reduced to 200 µg/plate with or without metabolic activation. For strain TA98 with metabolic activation, the maximum test concentration was reduced to 500 µg/plate. Narrowed concentration intervals were employed covering ranges from 0.8192 – 200 µg/plate or 2.048 – 500 µg/plate.
Vehicle	Dimethyl formamide (DMF)
Remarks - Method	Concentrations for main test were chosen based on the plate incorporation method conducted on TA100, TA102 and TA1535 (base-pair substitution type) and on TA98 and TA1537 (frameshift type) results. As the results of Experiment 1 were negative, treatments in the presence of S-9 in Experiment 2 included a pre-incubation step.

Tests with vehicle control and positive controls were run concurrently. Positive controls were:

- With metabolic activation: 2-aminoanthracene (TA100, TA1535 and TA1537) and benzo[*a*]pyrene (TA98)
- Without metabolic activation: 2-nitrofluorene (TA98); sodium azide (TA100, TA1535); 9-aminoacridine (TA1537) and mitomycin C (TA102).

The test substance was completely soluble in the aqueous assay system at all concentrations tested, in each of the experiments performed.

No major deviations from the test guideline were reported.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity	*Precipitation*	*Genotoxic Effect*
Absent			
Experiment 1	≥ 158	> 5,000	Negative
Experiment 2	≥ 200	> 200	Negative
Present			
Experiment 1	≥ 500	> 5,000	Negative
Experiment 2	≥ 500	> 500	Negative

Remarks - Results

The test substance, tested up to toxic concentrations in *S. typhimurium*, did not result in an increase of more than twice the number of revertant colonies in comparison to the negative control. In addition, no dose-related response was observed in any strains for base-pair substitution type or frame-shift type mutations, with or without metabolic activation.

The positive and negative controls provided a satisfactory response confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Covance (2012)

B.10. Genotoxicity – *in vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test

Cell Type/Cell Line: Human peripheral blood lymphocytes

Metabolic Activation System: Aroclor 1254 induced rat liver S9 mix

Vehicle: Dimethyl formamide (DMF)

Remarks - Method: Lymphocytes from the blood of three healthy, non-smoking male volunteers were used for each experiment.

The results of a cytotoxicity range-finder experiment were used to select suitable maximum concentrations for the main experiments.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Preliminary Test	0, 1.451, 2.419, 4.031, 6.718, 11.20, 18.66, 31.10, 51.84, 86.40, 144.0, 240.0, 400	3 h 20 h	20 h 20 h
Main Test 1	0, 1, 2, 4, 6, 8, 10, 12.50, 15*, 17.50, 20*, 30*, 40, 50	3 h	20 h
Main Test 2	0, 0.5, 1, 2, 4, 5, 6, 7, 8, 10*, 12.50*, 15*, 17.50, 20, 25, 30, 40	20 h	20 h

Present			
Preliminary Test	0, 1.451, 2.419, 4.031, 6.718, 11.20, 18.66, 31.10, 51.84, 86.40, 144.0, 240.0, 400	3 h	20 h
Main Test 1	0, 1, 2, 4, 6, 8, 10*, 12.50, 15, 17.50, 20*, 30, 40*, 50	3 h	20 h
Main Test 2	0, 0.5, 1, 2, 4*, 5, 6*, 7, 8, 10, 12.50*, 15*, 17.50, 20, 25, 30, 40	3 h	20 h

* Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Preliminary Test (3 h)	≥ 51.84	–	≥ 11.20	–
Preliminary Test (20 h)	≥ 31.10	–	≥ 11.20	–
Main Test 1	–	≥ 40.00	≥ 6.00	Negative
Main Test 2	–	> 40.00	≥ 15.00	Negative
Present				
Preliminary Test	≥ 31.10	–	≥ 18.66	–
Main Test 1	–	≥ 50.00	≥ 12.50	Negative
Mina Test 2	–	> 40.00	≥ 15.00	Negative

Remarks - Results

The positive and negative controls provided a satisfactory response confirming the validity of the test system.

Treatment of cultures in the absence and presence of S-9 resulted in frequencies of cells with structural aberrations that were similar to those observed in vehicle controls. Numbers of aberrant cells (excluding gaps) in all treated cultures in both experiments fell within the 95th percentile of the observed range.

Small, sporadic increases in the frequency of cells with numerical aberrations were observed in cultures treated with the test substance in the absence or presence of S-9. However, numerical aberrations were not assessed quantitatively and the assay is not specifically designed to evaluate the potential to induce polyploidy.

CONCLUSION

The notified chemical was not considered by the study authors to induce increases in the frequency of structural chromosome aberrations in cultured human peripheral blood lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY

Covance (2013g)

B.11. Genotoxicity – *in vitro* Mammalian Cell Gene Mutation Test – Hypoxanthine-Guanine Phosphoribosyl Transferase (HPRT)

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test

Cell Type/Cell Line: Mouse lymphoma cells/ L5178Y

Metabolic Activation System: Aroclor 1254 induced rat liver S9 mix

Vehicle: Dimethylformamide (DMF)

Remarks - Method: Tests with vehicle control and positive controls were run concurrently.

Positive controls were:

- With metabolic activation: benzo[*a*]pyrene
- Without metabolic activation: 4-nitroquinoline 1-oxide.

A 3 hour incubation period was used for all experiments.

No major deviations from the test guideline were reported.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*
Absent		
Preliminary Test	9.375, 18.75, 37.50, 75, 150, 300	3 h
Main Test 1	0.2*, 0.4*, 0.8*, 1.7*, 3.3*, 4.6*, 5.8*, 7.1, 8.3, 10.4, 12.5	3 h
Main Test 2	0.5*, 1*, 2*, 4*, 5*, 6*, 6.5, 7, 8, 9, 10	3 h
Present		
Preliminary Test	9.375, 18.75, 37.50, 75, 150, 300	3 h
Main Test 1	2.1*, 4.2*, 8.3*, 12.5*, 16.7*, 20.8*, 25.0*, 29.2*, 33.3*, 50.0*	3 h
Main Test 2	5*, 10*, 20*, 30*, 35*, 40*, 45, 50, 55, 60, 80	3 h

* Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Preliminary Test	≥ 9.375	–	≥ 37.50	–
Main Test 1	–	≥ 5.833	> 5.833	Negative
Main Test 2	–	> 6.00	> 6.00	Negative
Present				
Preliminary Test	> 75.00	–	≥ 37.50	–
Main Test 1	–	≥ 50.00	≥ 50.00	Negative
Main Test 2	–	> 40.00	≥ 40.00	Negative

Remarks - Results

The positive and negative controls provided a satisfactory response confirming the validity of the test system.

The highest concentrations selected for metaphase analysis in Experiment 1 were 5.833 µg/mL in the absence of S-9 and 50 µg/mL in the presence of S-9, with a relative cell survival of 12% and 40% observed, respectively.

The highest concentrations analysed for metaphase in Experiment 2 were 6 µg/mL in the absence of S-9 and 40 µg/mL in the presence of S-9, with a relative cell survival of 15% and 72% observed, respectively.

In Experiments 1 and 2, no statistically significant increases in mutant frequency were observed following treatment with the test substance at any concentration tested in the absence or presence of S-9 and there were no statistically significant linear trends.

CONCLUSION

The notified chemical was not considered by the study authors to be mutagenic to mouse lymphoma cells treated *in vitro* under the conditions of the test.

TEST FACILITY

Covance (2013h)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical oxygen demand (ThOD)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Test Substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	1.4	6	66.5
14	4.1	14	75.8
21	8.1	21	75.5
28	8.5	28	73.3

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 14 days (76%). Therefore, the tests indicate the suitability of the inoculums. Oxygen concentration in the inoculum blank did not exceed 1.5 mg/L during the test period. The residual concentrations of oxygen in the test bottles were greater than 0.5 mg/L during the test period. The percentage biodegradation in toxicity control at day 14 was 68% thus demonstrating that the notified chemical does not inhibit microbial degradation. The notified chemical attained 8.5% degradation after 28 days. Therefore, it cannot be considered to be readily biodegradable under the strict terms and conditions of OECD Test Guideline 301D.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Smithers (2013b)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Static
Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	88 mg $CaCO_3$/L
Analytical Monitoring	Total Carbon (TC) Analysis.
Remarks – Method	Due to the low aqueous solubility and complex nature of the test substance, a Water Accommodated Fraction (WAF) was prepared for the definitive test. A stock solution was prepared by adding 500 mg of the test substance to

5,000 mL of treated mains water and sonicating for 30 minutes to give a 100 mg/L stock solution WAF. Individual test concentrations were prepared by direct dilution from this stock solution.

The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration (mg/L) Nominal Loading Rate WAF	*Number of Fish*	*Mortality*				
		3 h	*24 h*	*48 h*	*72 h*	*96 h*
Control	7	0	0	0	0	0
0.625	7	0	0	0	0	0
1.25	7	0	0	0	0	0
2.5	7	1	7	7	7	7
5.0	7	7	7	7	7	7
10	7	7	7	7	7	7

LL50 1.8 mg/L at 96 hours WAF
NOEL 1.25 mg/L at 96 hours WAF

Statistical analysis was performed using linear interpolation (CETIS program v 1.8.6).

Remarks – Results All validity criteria for the test were satisfied. The dissolved oxygen was > 60% during the test.

Total Carbon analysis of the nominal 100 mg/L stock solution during the definitive test showed concentrations of carbon at 0 and 96 hours to be 56.0 and 60.6 mg/L, respectively. This is within 80 – 120% of the total carbon in 100 mg/L of the notified chemical. Therefore, the results are based on nominal concentrations.

CONCLUSION The notified chemical is toxic to fish.

TEST FACILITY Smithers (2013c)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test - Static
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 148 mg $CaCO_3$/L
Analytical Monitoring Total Carbon (TC) Analysis
Remarks - Method Due to the low aqueous solubility and complex nature of the test substance, a Water Accommodated Fraction (WAF) was prepared for the definitive test.

A stock solution was prepared by adding 50 mg of the test substance to 500 mL of treated mains water and sonicating for 30 minutes to give a 100 mg/L stock solution WAF. Individual test concentrations were prepared by direct dilution from this stock solution.

The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration (mg/L) Nominal Loading Rate WAF	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0	0
0.03	20	0	0
0.062	20	0	0
0.12	20	0	0
0.25	20	0	0
0.5	20	0	2
1.0	20	20	20

EL50	0.705 mg/L at 48 hours WAF (95% confidence limits: 0.651 – 0.735 mg/L)
NOEL	0.5 mg/L at 48 hours WAF
	Statistical analysis was performed using linear interpolation (CETIS program v 1.8.6).
Remarks - Results	All validity criteria for the test were satisfied.
	All validity criteria for the test were satisfied. The dissolved oxygen was > 60% during the test.
	Total Carbon analysis of the nominal 100 mg/L stock solution during the definitive test showed concentrations of carbon at 0 and 48 hours to be 53.0 and 45.6 mg/L, respectively. This is within 80 – 120% of the total carbon in 100 mg/L of the notified chemical. Therefore, the results are based on nominal concentrations.
CONCLUSION	The notified chemical is very toxic to aquatic invertebrates
TEST FACILITY	Smithers (2013d)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal loading rates of 0.010, 0.032, 0.10, 0.32 and 1.0 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Total Carbon (TC) Analysis.
Remarks - Method	Due to the low aqueous solubility and complex nature of the test substance, a Water Accommodated Fraction (WAF) was prepared for the definitive test.
	A stock solution was prepared by adding 100 mg of the test substance to 1,000 mL of treated mains water and sonicating for 30 minutes to give a 100 mg/L stock solution WAF. Individual test concentrations were prepared by direct dilution from this stock solution.
	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Biomass		*Growth*	
E_yL50 mg/L at 72 h (WAF)	*NOEL mg/L*	*E_rL50 mg/L at 72 h (WAF)*	*NOEL mg/L*
0.077	0.032	0.186	0.032

Remarks - Results

All validity criteria for the test were satisfied.

In the control, the cell density was increased by a factor of at least 16. The mean coefficient of growth rate in the control cultures did not exceed 35%. The coefficient of variation for average specific growth rates during the whole test period in replicate control cultures did not exceed 7%.

Total Carbon analysis of the nominal 100 mg/L stock solution during the definitive test showed concentrations of carbon at 0 and 72 hours to be 44.4 and 47.7 mg/L, respectively. This is within 80 – 120% of the total carbon in 100 mg/L of the notified chemical. Therefore, the results are based on nominal concentrations.

Statistical analysis was performed using linear interpolation (CETIS program v 1.8.6).

CONCLUSION

The notified chemical is very toxic to algae.

TEST FACILITY

Smithers (2013e)

C.2.4. Inhibition of Microbial Activity

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 209 Activated Sludge, Respiration Inhibition Test

Inoculum: Activated sludge

Exposure Period: 3 hours

Concentration Range: Nominal: 9.5, 30.5, 97.7, 312.5 and 1,000 mg/L

Remarks – Method

The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

Activated sewage sludge was exposed to the test substance at a loading rate of 9.5, 30.5, 97.7, 312.5 and 1,000 mg/L for a period of 3 hours at a temperature of 20 ± 2 °C with the addition of a synthetic sewage as a respiratory substrate.

3,5-Dicholorophenol was used as a reference substance.

RESULTS

EC50: 157.6 mg/L

NOEC: 9.5 mg/L

Mean inhibition of 15.84% was noted in the 9.5 mg/L treatment group. The inhibition noted was within normal variation (20%). Therefore, the NOEC was considered to be 9.5 mg/L.

Remarks – Results

All validity criteria for the test were satisfied.

The blank control respiration rate was ≥ 20 mg/g/h. The coefficient of variation of the blank control respiration rate was ≤ 30%. EC50 of the reference substance was between 2 and 25 mg/L for total respiration and between 5 and 40 mg/L for heterotrophic respiration and between 0.1 and 10 mg/L for nitrification respiration.

CONCLUSION	The notified chemical is not expected to inhibit microbial respiration.
TEST FACILITY	Smithers (2013f)

C.2.5. Acute Toxicity in Earthworms

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 222 Earthworms, Acute Toxicity Tests
Species	*Eisenia foetida*
Auxiliary solvent	None
Exposure Period	28 days adult worms 56 days for juvenile worms
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration mg/kg		*Number of Earthworms*	*Mortality (%)*
Nominal (mg/kg)	*Actual*		*28 days*
Control	Control	10	0
16.3	Not determined	10	0
308.6	Not determined	10	0
1,000	Not determined	10	0

LC50 (adult)	≥ 1,000 mg/kg at 28 days
NOEC (adult)	> 1,000 mg/kg at 28 days
NOEC (juvenile)	≥ 1,000 mg/kg at 56 days
Remarks - Results	The EC50 for the number of juveniles on Day 56 could not be estimated because there was not a dose-response relationship. All validity criteria for the test were satisfied. Each replicate (containing ten adults) produced ≥ 30 juveniles by the end of the test. The coefficient of variation of reproduction was ≤ 30%.
CONCLUSION	The notified chemical is not harmful to earthworms.
TEST FACILITY	Envigo (2016)

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