File No: STD/1534

June 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4-Octanol, 3-amino

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:

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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/1534	Brenntag Australia Pty Ltd	4-Octanol, 3-amino	Yes	≤ 50 tonnes per annum	Component of metal working fluids

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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 1B)	H314 – Causes severe skin burns and eye damage

The environmental hazard classification according to the *Globally Harmonised System for the 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 3)	H402 - Harmful to aquatic life

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

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

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

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Acute toxicity (Category 4): H302 – Harmful if swallowed
  - Skin irritation (Category 1B): H314 – Causes severe skin burns and eye damage

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following isolation and engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation if inhalation exposure is possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation processes:
  - Avoid contact with skin and eyes
  - Avoid inhalation
  - Have eye wash facilities available during reformulation processes

- 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 during reformulation process:
  - Coveralls, impervious gloves, eye protection and impervious footwear

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

- 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 for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- 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 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
- additional information on skin sensitisation becomes available.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from component of metal working fluids, 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 the notified chemical provided by the notifier was 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
Brenntag Australia Pty Ltd (ABN: 84 117 996 595)
260-262 Highett Road
HIGHETT VIC 3190

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, analytical data, degree of purity, impurities, additives/adjuvants and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: Acute dermal toxicity, acute inhalation toxicity and eye irritation studies

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

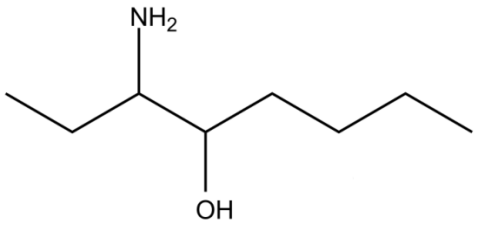
MARKETING NAME(S)
CORRGUARD EXT Amino Alcohol

CAS NUMBER
1001354-72-8

CHEMICAL NAME
4-Octanol, 3-amino-

MOLECULAR FORMULA
$C_8H_{19}NO$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
145.24 Da
ANALYTICAL DATA
Reference NMR, IR, GC and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 97%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: viscous colourless liquid or white/opaque solid (dried sample)

Property	Value	Data Source/Justification
Melting Point	21.5 °C	Measured
Boiling Point	217.9 °C at 101.3 kPa	Measured
Relative Density	0.89 at 20 °C	Measured
Vapour Pressure	5.8×10^{-3} kPa at 25 °C	Measured
Water Solubility	Distilled, deionised water: 4.3% at 25 °C pH 5: 4.4% at 25 °C pH 9: 4.2% at 25 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 1.2	Calculated. KOWIN v1.68, EPI Suite v4.1 (US EPA, 2010)
Surface Tension	52.5 mNm^{-1} at 25 °C	Measured
Adsorption/Desorption	< 0.3	Measured
Dissociation Constant	Not determined	Contains ionisable functionality and is expected to ionise under normal environmental pH range of 4-9
Flash Point	104 °C at 101 kPa	Measured
Flammability	Non-flammable	Measured
Autoignition Temperature	300 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties
Pyrophoric Properties	Not pyrophoric	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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical may be imported in to Australia as a bulk raw material at 85% concentration in water for reformulation within Australia or as a component of water-based metalworking fluid concentrates at 5-10% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	10-50	10-50	10-50	10-50	10-50

PORT OF ENTRY
Melbourne

TRANSPORTATION AND PACKAGING
The notified chemical as a raw material will be imported in dangerous goods compliant 200 kg steel drums or 1000 kg intermediate bulk containers (IBCs). It will be transported by road to warehouses where it will be stored

for reformulation at a later stage. The notified chemical as a component of fluid concentrates will be imported in plastic containers of various sizes, transported by road to warehouses or customer's sites for industrial use.

USE
The notified chemical will be used as a component of water-based metalworking fluids for ferrous metal corrosion control. The notified chemical will be used only by professionals under industrial settings and is not intended for use by the general public.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. It may be imported as a blended bulk raw material for reformulation or as a component of metalworking fluid concentrate.

Reformulation
The notified chemical in bulk as a raw material will be reformulated using a closed liquid blending process. This will involve the notified chemical being pumped into the blending tank using automated pumping/dosing equipment with quick connect fittings used to attach the pipes/hoses to the import containers. During the blending step, the blending vessels will remain closed and supplied with local fume extraction. Regular sampling of the blend mixture for the purpose of quality control will be done during the blending process from a sampling port. Once blending is complete, the reformulated metalworking fluid concentrate containing the notified chemical at up to 10% concentration will be gravity fed to an automated filling machine for distribution into containers of various sizes.

End-use
The fluid concentrates containing the notified chemical at 5-10% concentration will be diluted in water to a final use concentration of 0.2-0.5% for industrial use in metalworking/forming mills and lathe unit operations. The notified chemical in fluid concentrate (5-10% concentration) will be added to the make-up tank for use. This will be diluted in the make-up tank and pumped directly to the enclosed metalworking machinery. Within the machine, the fluid will be coated onto the metal surface either using spray or rollers. Excess fluid will drip down into the sump and be reused. Residual fluid from the surface of the processed metals will be removed with the aid of a high velocity air blast prior to the manual removal of the processed metal from the machine. During maintenance of metalworking machinery, the fluid will be drained and sent to a liquid waste treatment facility.

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	4	30
Plant operators – Reformulation & equipment maintenance	5	12
Plant operators – quality control	2	12
Plant operators – metalworking machine and/or lathe unit	4-12	200

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may be exposed to the notified chemical during the loading and off-loading of containers containing it at up to 10% concentration (metalworking fluid concentrates) or 85% concentration (bulk raw material). Workers would only be exposed to the notified polymer in the event of an accident. The transfer facilities are expected to be well-ventilated with control systems for accidental spills, minimising the risk of worker exposure to the notified polymer during these stages.

Reformulation
Dermal and ocular exposure to the notified polymer (up to 85% concentration) is possible when plant operators are connecting and disconnecting pump lines to storage tanks or blending vessels. The notifier anticipates that the blending facilities will be fully automatic and enclosed systems with ventilation and control systems in place for accidental spills and wastewater treatment. Quality control workers will come into contact with the notified

chemical during sampling of the chemical mixture for quality control. Equipment maintenance workers may come into contact with the notified chemical during the cleaning and maintenance of the machine. The blending machine is expected to be flushed through with solvent to remove any residual chemical prior to maintenance/repair. Transfer of the finished lubricant containing the notified polymer at ≤ 10 % concentration to packaging will be performed using automated processes; exposure to workers is not expected. The use of personal protective equipment (PPE) such as coveralls, safety glasses, impervious gloves and boots by the workers along with proper training in handling of the notified chemical and a high degree of automation should minimize the workers' exposure to the notified chemical.

Sampling
At reformulation facilities samples may be taken from blending vessels for quality assurance testing. Dermal exposure to the notified polymer (up to 100% concentration) may occur during sampling. To minimise exposure, the notifier states that QA staff are expected to wear gloves, eye protection and long sleeved lab coats.

End use
Plant operators using the metalworking machinery and/or lathe units may come into contact with the notified chemical at up to 10% concentration. The exposure may occur during the manual transfer of the metalworking fluid concentrates from container into the make-up tank or during the cleaning and maintenance of equipment. The notifier anticipates that the processes will be mostly enclosed or supplied engineering controls such as shielding and local ventilation to reduce exposure from splashes, mists and vapours. The notifier states that exposure will be minimised by the use of personal protective equipment (PPE) such as coveralls, safety glasses, impervious gloves and boots by the workers.

6.1.2. Public Exposure
The notified chemical will not be used by the public. Indirect exposure to the notified chemical is unlikely as the chemically treated metals will either be cleaned or contained within manufactured/assembled machinery by the time the manufactured goods reach the public.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 = 550 mg/kg bw; harmful
Rabbit, skin irritation	corrosive
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation; EC3 = 21%
Skin sensitisation *(in chemico)* – Direct Peptide Reactivity Assay	negative for skin sensitisation
Skin sensitisation (*in vitro)* - ARE-Nrf2 Luciferase Assay*	negative for skin sensitisation
Rat, repeat dose dermal toxicity – 14 days.	NOEL = 200 mg/kg bw/day (Male) 100 mg/kg bw/day (Female)
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 60 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days.	NOAEL = 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration test	non genotoxic
Genotoxicity – in vivo mouse micronucleus test	non genotoxic
Rat, reproductive and developmental toxicity	NOAEL = 150 mg/kg bw/day
Rat, prenatal developmental toxicity	NOAEL = 150 mg/kg bw/day (developmental) 15 mg/kg bw/day (maternal)
In vitro percutaneous absorption	51.4 ± 8.9% at 0.5% concentration 20.6 ± 10.3% at 10% concentration

* - only study summary provided

Toxicokinetics, metabolism and distribution
A percutaneous absorption study done in vitro on human skin using the notified chemical demonstrated that the chemical is readily absorbed with absorption of 51% at 0.5% concentration and 21% at 10% concentration.

Acute toxicity
The notified chemical was found to be harmful in an acute oral toxicity study in rats with a LD50 of 550 mg/kg body weight. No acute dermal and inhalation toxicity studies were provided for the notified chemical.

Irritation
Dermal irritation studies carried out on rabbits indicated that the notified chemical both with the pH adjusted and unadjusted (PSL, 2007c) was corrosive to the skin with severe erythema, oedema and corrosion observed when the test substance was applied for 1 hour. No eye irritation study was conducted due to the corrosive nature of the notified chemical.

Sensitisation
A skin sensitisation study conducted with the notified chemical on Guinea pigs (challenge concentration 50%; Magnusson and Kligman test) showed no signs of sensitisation.

The notified chemical was found to be a skin sensitizer in a local lymph node assay (LLNA) in mice, with reported stimulation indices of 1.5, 2.5 and 28.8 at 5%, 20% and 80% concentration, respectively. The calculated EC3 value was reported to be 21%.

One *in chemico* and one *in vitro* assay addressing the adverse outcome pathway (AOP) leading to skin sensitisation were also conducted to evaluate the sensitisation potential of the notified chemical. The test substance did not reduce the level of free peptide in the Direct Peptide Reactivity Assay (DPRA) assay suggesting it is unable to interact with the test peptide thus is unlikely to interact with skin proteins. Similarly in the ARE-Nrf2 Luciferase Assay, no test substance mediated increase in the expression of luciferase gene under the control of the antioxidant response element (ARE) was noted suggesting the test substance is not capable of activating keratinocytes. Based on the results of the assays, the notified chemical is not likely to be a sensitiser.

When considering the full weight of evidence it is unlikely that the notified chemical is a sensitiser and the LLNA study result may be a false positive. Corrosive chemicals can produce false positive results in the LLNA assay (OECD TG 429).

Repeated dose toxicity

14-day dermal toxicity
A 14-dermal toxicity study was conducted on F344/DuCrl strain rats. The notified chemical was diluted in propylene glycol at 50, 100 and 150 mg/ml concentrations and 1 ml and 4 ml /kg bw of these concentrations were applied giving final doses of 50, 100, 150, 200, 400 and 600 mg/kg bw of test substance.

Test animals exposed to 150, 400 and 600 mg/kg bw/day of test substance all showed various degrees of burns at different stages of the study and were immediately euthanized. The test substance when applied at 200 mg/kg bw/day at a lower concentration of 50 mg/mL, 4 ml/kg bw resulted in scaling on day 11 in female rats only. The male rats exposed to 200 mg/kg bw/day of test substance at the lower concentration did not show any signs of dermal toxicity.

A No Observed Effect Level (NOEL) for dermal effects of the notified chemical was established as 100 mg/kg bw/day for female rats and 200 mg/kg bw/day for male rats.

28-day oral toxicity
The notified chemical was administered at concentrations of 20, 60 and 250 mg/kg bw/day by oral gavage for 28-days to Crl:WI(Han) strain rats (Notox 2007).

One male rat from 20 mg/kg bw/day dose group was found dead on day 24. Macroscopic findings suggested the cause of death to be due to gavage error. No clinical signs of toxicity were observed with any test group during the course of the study. No treatment related effects were observed on body weight gains, food consumption and functional observations.
Clinical laboratory investigations showed treatment related increase in haemoglobin, red blood cell count, haematocrit levels, alanine aminotransferase activity, alkaline phosphatase activity, glucose, calcium and potassium levels in female rats exposed to 250 mg/kg bw/day of test substance. Male rats from the 250 mg/kg bw/day group showed increased alanine aminotransferase activity, alkaline phosphatase activity, glucose, calcium, inorganic phosphate and potassium levels.

Histopathological examination of the spleen showed a slightly increased haemopoiesis in rats from 60 and 250 mg/kg bw/day dose groups. The mean liver weight in male rats from 250 mg/kg bw/day group was high compared to control.

Based on the adverse effects seen at 250 mg/kg bw/day in Crl:WI(Han) strain rats, a No Observed Adverse Effect Level (NOAEL) of 60 mg/kg bw/day was established.

90-day oral toxicity
The notified chemical was administered at concentrations of 15, 60 and 150 mg/kg bw/day by oral gavage for 90-days to Crl:CD(SD) strain rats of both sexes. For comparison, Crl:WI(Han) strain male rats were also included in the study and were exposed to 150 mg/kg bw/day of the notified chemical.

Crl:CD(SD) strain rats –No toxicologically significant treatment related effects were noted, and hence a NOAEL of 150 mg/kg bw/day (the highest dose tested) was established by the study author.

Crl:WI(Han) strain rats – only limited tests were done on the rats. Clinical signs such as noisy, slow, laboured respiration with mouth breathing, reflux of test substance and / or blood coming from the nasal cavity were observed in six of ten rats exposed to 150 mg/kg bw/day of test substance. A significant increase in the relative weight of epididymides was observed. Based on the adverse effects seen at 150 mg/kg bw/day and no lower dose tested, a NOEL/NOAEL value could not be established in the study for Crl:WI(Han) strain rats.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in an in vitro bacterial mutation test. The notified chemical did not demonstrate any clastogenic potential to rat lymphocytes. The notified chemical was not clastogenic when test in vivo in a mouse peripheral blood micronucleus test.

Toxicity for reproduction

Reproduction and Developmental Toxicity
A study was conducted to assess the potential of the notified chemical to induce reproduction and developmental toxicity in Crl:CD(SD) rats. Groups of twelve male and female rats were exposed to the notified chemical at 15, 60 and 150 mg/kg bw/day concentrations by oral gavage.

No treatment related effects were observed on behaviour, weight gain, reproductive indices, time of mating, gestational length, post-implantation loss, pup survival and sex ratio. No treatment related changes in pup body weight and size were observed at any dose levels. Based on the absence of adverse effects seen at highest tested dose a NOAEL of 150 mg/kg bw/day was established.

Prenatal Developmental Toxicity
A study was conducted to assess the potential of the notified chemical to induce maternal and developmental toxicity using Crl:CD(SD) strain rats. Groups of 24 time mated female rats were exposed to the notified chemical at concentrations of 15, 60 or 150 mg/kg bw/day by oral gavage from gestational day 6 (implantation day) to gestational day 20.

Treatment related decreases in maternal body weight gains of 33.6% and 50.4% were observed in rats from 60 and 150 mg/kg bw/day dose groups respectively from gestational days 6 to 9. Feed consumption was also reduced in these groups from gestational days 6 to 12. No treatment related developmental toxicity was observed in the foetuses from any dose group.

The NOAEL for developmental toxicity was established as 150 mg/kg bw/day, the highest dose tested in this study, based on the absebce of adverse effects at this dose. The NOEL for maternal toxicity was established as 15 mg/kg bw/day based on the decrease in weight gain and feed consumption seen at higher doses of 60 and 150 mg/kg bw/day.

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

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 1B)	H314 – Causes severe skin burns and eye damage

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

The notified chemical causes severe skin burns and eye damage and is harmful following acute oral exposure. Therefore adverse effects may occur unless controls have been put in place to limit worker exposure.

Dermal and ocular exposure of workers to the notified chemical at concentrations of up to 85% may occur during transport, reformulation and end use. Exposure will be minimised by the use of automated and enclosed processes and PPE.

Overall, provided engineering controls are instituted, workers wear appropriate PPE, and safe work practices are maintained to reduce exposure, the risk to workers is not considered to be unreasonable.

6.3.2. Public Health

The notified chemical is for industrial use only. The public will not come into contact with the notified chemical and therefore the risk to the public is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia. However, the notified chemical will be imported as a raw material for local reformulation or as a component of concentrated water-based metal working fluids. Blending is expected to take place in fully-contained, industrial facilities. The potential for spills and leaks during transport, storage and blending are expected to be low (up to 2% of the total import volume). Spills of the waste metal working fluids are expected to be contained within bunds and reclaimed or sent to on-site waste treatment facilities before being released to the sewage system. Wastewater containing the notified chemical is expected to undergo pond aeration and biological treatment during on-site treatment processes.

RELEASE OF CHEMICAL FROM USE

The finished metal working fluids containing the notified chemical will be used at industrial sites. Release may occur from spills during pumping of the concentrate from the transport containers to the make-up tank and from connection and disconnecting hoses. However, spills from these activities are expected to be very limited (0.5% of the total import volume). The diluted metal working fluid will be circulated through contained systems until they are spent. Spent metal working fluids (up to 90% of the notified chemical) are expected to be drained, drummed off and disposed of to a liquid waste treatment facility.

RELEASE OF CHEMICAL FROM DISPOSAL

Residues in empty containers and some of the collected spills are expected to be disposed of to landfill while spent diluted metal working fluids are expected to be collected for disposal to a wastewater treatment facility.
At the waste treatment facility any oil phase will be separated in an API process. The water-soluble phase will be subjected to pond aeration and biological treatment before being released to the sewage system.

7.1.2. Environmental Fate

The notified chemical is expected to be readily biodegradable based on the environmental fate study. For the details of the environmental fate studies please refer to Appendix C. The notified chemical is not expected to partition to the air compartment based on its low vapour pressure (5.8 Pa). The majority of notified chemical is expected to be released to wastewater from discharge of spent metal working fluids. Wastewater is expected to be collected and treated by a waste water treatment facility before being released to the sewer. During treatment, most of the notified chemical is expected to be removed given it is readily biodegradable (105.5% over a 28 day test period). Despite the expected efficient removal during wastewater treatment processes, a small amount of notified chemical may be released to receiving waters. However, the notified chemical is

expected to disperse and degrade. Bioaccumulation is not expected due to its high water solubility and low water/octanol partition coefficient (log Pow = 1.3). Sludge from wastewater treatment plants which may contain a limited amount of the notified chemical is expected to be disposed of to landfill or applied to agricultural soils. Notified chemical in landfill or soil is expected to be mobile based on its estimated low soil adsorption coefficient (log K_{oc} < 0.3). However, in landfill, soil and water, the notified chemical is expected to rapidly degrade into water, and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

Wastewater streams receiving the spent notified chemical may be directed to sewers. Therefore, under a worst case scenario, it is assumed that 100 % of the total import volume of the notified chemical will be discharged into sewers over 260 days per year corresponding to release only on working days. The predicted environmental concentration (PEC) can be estimated as outlined below.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	50,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	50,000	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	192.31	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	42.25	µg/L
PEC - Ocean:	4.25	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 42.5 µg/L may potentially result in a soil concentration of approximately 283.5 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 1.42 mg/kg and 2.83 mg/kg, respectively.

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 Toxicity		
Fish	LC50 (96 hours) = 68 mg/L	Harmful to fish
Daphnia	EC50 (48 hours) = 44 mg/L	Harmful to aquatic invertebrates
Algal	E_rC50 (72 hours) = 39 mg/L	Harmful to algae
Chronic Toxicity		
Fish	NOEC = 103 mg/L	Not harmful to fish on a chronic basis

Based on the acute toxicity for fish, daphnia and algae, the notified chemical is formally classified as “Acute Category 3: Harmful to aquatic life” under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009). On the basis of the chronic toxicity and the lack of ready biodegradability, the notified chemical is not formally classified under GHS for long-term hazard.

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 for the most sensitive species (algae, E_rC50) for the notified chemical. Three acute ecotoxicity endpoints for aquatic species from three trophic levels are available. Therefore, an assessment factor of 100 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
E_rC50 (Invertebrates)	39	mg/L
Assessment Factor	100	
PNEC:	390	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River	42.25	390	0.109
Q - Ocean	4.25	390	0.011

The Risk Quotients (Q = PEC/PNEC) for the worst case scenario have been calculated to be << 1 for the river and ocean compartments. Although the notified chemical may be released into waterways, it is not expected to pose a significant risk to the aquatic environment as ecotoxicologically significant concentrations are unlikely to be reached under this assessed scenario. The notified chemical is expected to rapidly degrade in the environment and bioaccumulation is not expected. Therefore, on the basis of the PEC/PNEC ratio and the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 21.5 °C

Method	Visual assessment
Remarks	The value is an average of 2 independent tests which gave 21°C and 22 °C
Test Facility	Intertek (2007)

Boiling Point Method 1: 217.9 ± 0.2 °C at 101.3 kPa
Method 2: 186.2 ± 2.5 °C at 56.5 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Method 1: Visual assessment using a melting point/boiling point apparatus Method 2: Measurement done using ebulliometer
Test Facility	Intertek (2007)

Relative Density Method 1: 0.89 ± 0.01 at 30 ± 0.5 °C
Method 2: 0.89 ± 0.01 at 20 ± 0.5 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Method 1: Pycnometer method. Measurement done in duplicate Method 2: Automatic density meter. Measurement done in duplicates
Test Facility	Intertek (2007)

Vapour Pressure 2.8×10^{-3} kPa at 20 °C
5.8×10^{-3} kPa at 25 °C

Method	EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Measurements done in triplicates
Test Facility	Intertek (2007)

Water Solubility Distilled, deionised water: 4.3% at 25 °C
pH 5: 4.4% at 25 °C
pH 9: 4.2%25 °C

Method	Not mentioned, similar to OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method
Test Facility	Intertek (2007)

Surface Tension 52.5 mN/m at 25 °C

Method	EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Concentration: 0.1 g was dissolved in 100 mL of water. Wilhelmy plate method
Test Facility	Intertek (2007)

Partition Coefficient (n-octanol/water) log Pow = 1.3 at 25 °C

Method	Estimation of Log P of Test Substance Using individual n-Octanol and Water Solubility
Remarks	Due to the surface active nature of the test substance, the log P has been estimated from the individual solubilities of the test substance in distilled, deionised water (shake-flask method) and n-octanol.
Test Facility	Intertek (2007)

Adsorption/Desorption – screening test log $K_{oc} < 0.3$

Method	OECD TG 121: Estimation of the Adsorption Coefficient (K_{oc}) on Soil and Sewage using a High Performance Liquid Chromatography Method.

Remarks	In the HPLC assay for determining the K_{oc}, the test substance was not retained on the HPLC column under the analysis conditions, and eluted prior to the reference compounds. Therefore, the estimated log K_{oc} value for the test substance was estimated to be < 0.3.The temperature of the HPLC column during the series of HPLC analyses ranged from 18.6 to 21.8 °C.
Test Facility	TERC (2008)

Flash Point 104 ± 5 °C at 101 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Measurements done in duplicate.
Test Facility	Intertek (2007)

Flammability Not flammable

Method	EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water).
Test Facility	Intertek (2007)

Pyrophoric Properties Not Pyrophoric

Method	EC Council Regulation No 440/2008 A.13 Flammability
Test Facility	Intertek (2007)

Autoignition Temperature 300 ± 10 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	The test was carried out with 5 °C increments instead of 2 °C increments.
Test Facility	Intertek (2007)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified Chemical

METHOD: OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure.
- Species/Strain: Rat/Fischer 344
- Vehicle: None
- Remarks - Method: No significant protocol deviations. Six female rats were used for the study and dosed sequentially based on the survival of the previous rat in the short-term period following dosing. The pH of the test substance tested was 12.5.

RESULTS

Dosing Sequence	Animal No.	Dose Level (mg/Kg bw)	Short-Term Outcome	Long-Term Outcome
1	01	175	Survival	Survival
2	02	550	Death	Death
3	03	175	Survival	Survival
4	04	550	Survival	Survival
5	05	2,000	Death	Death
6	06	550	Death	Death

- LD50: 550 mg/kg bw with a 95% profile likelihood confidence interval of 88.94 mg/kg bw (lower) and 2,430 mg/kg bw (upper)
- Signs of Toxicity: Two animals exposed to 550 mg/kg bw of test substance died within one day of administration, the animal dosed with 2,000 mg/kg bw of test substance died within 2 hours of administration of the test substance. The rest of the animals survived till the end of the study period of 14 days.
  All the animals exposed to 550 mg/kg bw of test substance showed clinical signs of toxicity such as hypoactivity, prone posture and / or ocular discharge. The animal that survived, recovered from the above-mentioned symptoms by day 3. The animal exposed to 2,000 mg/kg bw of test substance showed hypoactivity, hunched posture and piloerection.
- Effects in Organs: Gross necropsy of the animals that died during the study revealed discoloration of the intestines.
- Remarks - Results: All surviving animals gained weight throughout the study.

CONCLUSION: The notified chemical is harmful via the oral route.

TEST FACILITY: PSL (2007a)

B.2. Irritation – skin

TEST SUBSTANCE: Notified Chemical (pH adjusted to 9.5 with concentrated HCl)

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion.
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 1
- Vehicle: None
- Observation Period: 1 hour after patch removal
- Type of Dressing: Semi-occlusive.
- Remarks - Method: No significant protocol deviations.

RESULTS

- Remarks - Results: Initial testing conducted on one rabbit at three different sites. 200 µl of the test substance was applied and left for 3 minutes (1 site) and 1 hour (2

sites). One hour after patch removal, moderate/severe erythema, slight oedema and a dark brown area were noted at the 3 minute dose site. Severe erythema, slight oedema and corrosion were noted at the 1 hour site immediately after patch removal. Due to corrosion noted at the 1 hour site, the study was terminated and the animal was euthanized for humane reasons.

CONCLUSION The notified chemical is corrosive to the skin.

TEST FACILITY PSL (2007b)

B.3. Skin sensitisation

TEST SUBSTANCE Notified Chemical (pH adjusted to 9.5 with concentrated HCl)

METHOD OECD TG 406 Skin Sensitisation – Magnusson and Kligman Test.
Species/Strain Guinea pig/Albino, NIH(Dunkin Hartley)
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 1%
topical: 75%
MAIN STUDY
Number of Animals Test Group: 10F & 10M Control Group: 5F & 5M
INDUCTION PHASE Induction Concentration:
intradermal: 3%
topical: 75%
Signs of Irritation Slight erythema with a score of 0.5 was observed in 17 animals at 1 and 24 hour observation after topical application of the test substance.
CHALLENGE PHASE Challenge Concentration:
topical: 50%
Remarks - Method No significant protocol deviations. Distilled water was used as vehicle control.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*	
		24 h	*48 h*
Test Group	50%	0/20	0/20
Control Group	50%	0/10	0/10

Remarks - Results There were no deaths or test substance-related clinical signs of toxicity or remarkable body weight changes during the study. There were no reactions indicative of sensitisation to the test substance following the challenge exposure.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY Advinus (2010)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified Chemical (pH adjusted to 9.5 with concentrated HCl)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/J
Vehicle Propylene Glycol
Remarks - Method No significant protocol deviations. A screening study was conducted using the test substance at 0.05, 0.1, 0.5, 2.5, 5.0 and 10% concentrations to evaluate its irritancy potential as measured by erythema on the ears. No erythema was observed and hence higher concentrations of 20, 40 and

80% were evaluated, with no signs of irritation observed.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	188	
5%	280	1.5
20%	477	2.5
80%	5,420	28.8
Positive Control		
30% α-Hexylcinnamaldehyde	3,211	17.1

Remarks - Results

There were no mortalities and no signs of systemic toxicity noted for the test and control animals.
Mice treated with test substance at 80% demonstrated slight erythema on day 3 and day 6. The positive control elicited a stimulation index of 17.1 when compared to vehicle only treated mice.
A stimulation index of > 3 was recorded for the test substance at 80% concentration. Based on these results the EC3 value is calculated to be 21%.

CONCLUSION

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

TEST FACILITY

TERC (2007a)

B.5. *In Chemico* Skin Sensitisation (DPRA Test)

TEST SUBSTANCE

Notified chemical

METHOD

Direct Peptide Reactivity Assay (DPRA)

Remarks - Method

The test was conducted before the introduction of the OECD test guideline for DPRA (OECD TG 442c). The test substance was prepared in acetonitrile (8mM stock solution). Hydrochinon (strong sensitiser) and isoeugenol (moderate sensitiser) were used as positive controls. A model N-terminal acetylated hepta-peptide containing 1 cysteine and 2 lysine residues (amino acid sequence - Ac-NKKCDLF) prepared in acetonitrile was used. 0.266mM stock solutions of the peptide were prepared in phosphate buffer pH 7.4 and 10.0.

The test substance was mixed with the model peptide in two different assay buffers (pH 7.4 and pH 10.0) and incubated at 37 °C for up to 24 hours. Samples were collected at various time points (0, 1, 2, 3, 5 and 24 h) to measure depletion of free peptide. The content of free cysteine was determined in mixture at pH 7.4 and was determined by measuring the reaction of the sulfohydrile group with monobromobinane leading to a fluorescence product. The content of free lysine was determined in mixture at pH 10.0 and was determined by the quantitative analyses of the free peptide using LC-MS multiple ion scan techniques. Additionally the oxidised and dimerised peptides were semi-quantified and the potential to form stable adducts was evaluated.

RESULTS

Remarks - Results

No peptide depletion was observed at any time point in samples incubated with the test substance. Marked reduction in free peptide was observed in samples containing positive controls. With the strong sensitiser hydrochinon total depletion of free peptide was observed within 5 hours. Approximately 80% reduction in free peptide was observed with isoeugenol at 24 hour.

CONCLUSION The test substance was considered not to react with endogenous proteins within the skin to induce sensitising effects.

TEST FACILITY Harlan-CCR (2010)

B.6. Repeat dose dermal toxicity

TEST SUBSTANCE Notified Chemical (pH adjusted to 9.5 with concentrated HCl)

METHOD Repeated Dose Dermal Toxicity: 14-day Study
Species/Strain Rat/F344/DuCrl
Route of Administration Dermal – semi-occluded
Exposure Information Total exposure days: 14 days
Dose regimen: 5 days per week
Duration of exposure: 6 hours/day
Post-exposure observation period: 24 hours
Vehicle Distilled water
Remarks - Method The study protocol was in line with the OECD TG 410 protocol. The parameters evaluated included cage-side observations, dermal observations, body weights and body weight gains. No histopathological and biochemical tests were conducted.

RESULTS

Group	*Dose*	*Number and Sex of Animals*	*Dose solution Concentration (mg/ml)*	*Volume applied (ml/kg bw)*	*Actual Dose mg/kg bw/day*	*Dose level (%)*	*Mortality*
A	Vehicle	3F & 3M	0	1	0	0	0/6
A	Low	3F & 3M	50	1	50	5	0/6
A	Mid	3F & 3M	100	1	100	10	0/6
A	High	3F & 3M	150	1	150	15	6/6
B	Vehicle	3F & 3M	0	4	0	0	0/6
B	Low	3F & 3M	5	4	200	5	0/6
B	Mid	3F & 3M	100	4	400	10	6/6
B	High	3F & 3M	150	4	600	15	6/6

Mortality & other Observations
The mortality figures above represent the number of rats that were euthanized due to severe erythema and burns observed between day 1 and day 4 of application of the test substance.

Remarks – Results
Group A
Two male rats in high dose group (150 mg/kg bw/day) were noted with very slight erythema on test day 2, increasing to one male rat having very slight erythema and two male rats had well-defined erythema on test day 3. After dosing on test day 4, one male rat was noted with very slight erythema and the remaining two males were noted with severe erythema and burns and hence all the male rats from this group were euthanized on test day 4. All the female rats from high dose group had slight scaling following the 6 h dosing period on test day 11 (final day). On test day 12, two female rats had slight erythema and burns of the dermal test site leading to all 3 female rats in high dose group being euthanized on test day 12.

There were no dermal observations noted for any animal in the vehicle, low (50 mg/kg bw/day) and mid (100 mg/kg bw/day) dose groups throughout the study.

Group B
On test day 1, following single 6 h dosing period, all males and one female from high dose group (600 mg/kg bw/day) had burns at the dermal test site and hence all the animals from this dose group were immediately euthanized.

All the 3 male rats dosed with 400 mg/kg bw had very slight to slight erythema, very slight oedema and burns

of the dermal test site following the 6 h dosing on test day 2. The 3 male rats were euthanized on test day 2. All 3 female rats in this dose group had very slight oedema on test day 2 and very slight erythema and oedema on test day 3. These females had very slight oedema and slight to severe erythema, and 2 of the 3 females had burns of the dermal test site following the 6 h dosing period one day 4. All 3 female rats in this dose group were euthanized on test day 4.

Slight scaling was observed in all 3 female rats dosed at 200 mg/kg bw following the 6 h dosing period on test day 11. There were no dermal observations noted for any vehicle animals or for male rats in the low dose group (200 mg/kg bw/day) throughout the study.

CONCLUSION
The No Observed Effect Levels (NOEL) were established as 200 mg/kg bw/day for male rats and 100 mg/kg bw/day for female rats in this study, based on the adverse skin reactions seen at higher doses.

TEST FACILITY TERC (2007b)

B.7. Repeat dose 90-day oral toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain Rat/Crl:CD(SD) and Rat/Crl:WI(Han)
Route of Administration Oral – gavage
Exposure Information Total exposure days: 90 days
Dose regimen: 7 days per week
Post-exposure observation period:
Vehicle Propylene glycol
Remarks - Method No significant protocol deviations.
Epididymal sperm parameters (sperm count, motility and morphology) were also tested to definitively support or refute the test effects seen in reproduction/developmental toxicity study conducted using Crl:WI(Han) strains rats and to determine if the findings from the reproductive/ developmental toxicity study were strain specific. The dose solutions were not corrected for purity.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control[1]	10F & 10M	0	0/20
low dose[1]	10F & 10M	15	2/20
mid dose[1]	10F & 10M	60	0/20
high dose[1]	10F & 10M	150	3/20
control[2]	10M	0	0/10
high dose[2]	10M	150	0/10

[1]Crl:CD(SD) strain and [2]Crl:WI(Han) strain

Mortality and Time to Death
Crl:CD(SD) strain rats
Two female rats from the low dose group died on day 5 and 10 and 3 female rats from high dose group died spontaneously on day 6, 8 and 9. The deaths were reported to have occurred due to gavage errors.

Crl:WI(Han) strain rats
All animals survived the study.

Clinical Observations
Crl:CD(SD) strain rats
Compared to control, test substance treated rats exhibited no change in sensory activity, body temperature (rectal measurement), grip performance, motor activity, ophthalmology and food consumption. At the end of the study period the body weight of male rats from test groups were slightly lower than control group but the

difference did not reach a statistical significance. No changes in body weight and body weight gain were observed with female rats.

Crl:WI(Han) strain rats

Six of ten animals from the high dose group showed noisy respiration, slow respiration, laboured respiration with mouth breathing, reflux of test substance and /or blood coming from the nasal cavity. The observations were associated with irritancy of the test substance. Treatment related reduction in body weight and body weight gain was also observed when compared to control group. The reduction was significant with 4.3 – 7.0% reduction in body weight and 7.0 – 16.8% reduction in body weight gain. There was also a slight but significant reduction (5.2 – 6.3%) in feed consumption relative to controls between test days 1 – 8 & 9 – 15.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Crl:CD(SD) strain rats

One male rat in the low dose group had higher reticulocyte count, higher MCV and lower erythrocyte count suggesting regenerative anaemia. The rat also had lower leukocyte counts and the terminal body weight was also less. The effects observed were suggested to be not test substance related by the study author due to a single incidence and lack of dose response. The mean urea nitrogen in mid dose group and the mean alkaline phosphatase value in high dose group were significantly higher than control. However the findings were considered unrelated to the treatment by the study author due to lack of dose response relationship.

Urinalysis data showed minimal and significant increase in urine volume in male and female rats respectively with a corresponding decrease in urine specific gravity. However, as there were no other indications of renal toxicity, these findings were considered likely to be due to the alcohol in the test substance by the study author. There was a slight dose-related increase in the incidence of higher urine pH that was attributed to excretion of the alkaline test material.

Crl:WI(Han) strain rats

No tests were conducted.

Effects in Organs

Crl:CD(SD) strain rats

Female rats in the high dose group showed a statistically significant increase in liver body weight of 14% when compared to control. Absolute brain weights were significantly higher in the low dose group rats; however these were deemed not toxicologically significant by the study author due to the lack of dose-response relationship and no change in relative brain weights.

Crl:WI(Han) strain rats

A significant increase in the relative weight of the epididymides was seen in high dose group when compared to controls. The sperm parameters were not affected in these rats. No other histopathological changes were noted.

Remarks – Results

Based on the low level of changes seen and lack of dose-response relationship, the study author considered the effects toxicologically insignificant.

CONCLUSION

A No Observed (Adverse) Effect Level (NO(A)EL) was established as 150 mg/kg bw/day, the highest dose tested in this study for Crl:CD(SD) strain rats, based on the absence of adverse effects seen at this dose.

TEST FACILITY TERC (2010)

B.8. Reproduction and Developmental toxicity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 421 Reproduction/Developmental Toxicity Screening Test.
Species/Strain	Rats/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Exposure days: 52 days in female and 33 days in male
Vehicle	Propylene glycol

Remarks - Method No significant protocol deviations. The test animals were dosed once daily with the female rats for 2 weeks prior to breeding, during breeding (2 weeks), 3 weeks gestation and for 4 days during the lactation period. male rats were dose 2 weeks prior to breeding and during breeding (2 weeks) until necropsy.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	12F & 12M	0	0/24
Low dose	12F & 12M	15	1/24
Mid dose	12F & 12M	60	0/24
High dose	12F & 12M	150	2/24

Mortality and Time to Death

One male rat from low dose was found dead on test day 11 and one female rat from high dose was found dead on test day 40. Gross pathological observations of the male rat in low dose group indicated froth in the trachea, bloody facial soiling and mottled lungs. Gross pathological examinations of the female rat in high dose group revealed mottled lungs and a pregnant uterus containing five normal appearing foetuses. Histopathological examinations of the tissues taken from the female rat indicated severe fibrinopurulent inflammation of the larynx and trachea. These findings on both the rats suggested an error in gavage as the probable cause of death.
One male from the high dose group had a mechanical injury to the oral cavity associated with maloccluded incisors on test day 29 and was subsequently euthanized.

Effects on Dams

All animals except the above survived the study. No treatment related effects on behaviour were observed. There was an increased incidence of noisy respiration in the high dose group female rats during the lactation phase of the study. These finding did not have a gross pathologic correlate and thus were not considered treatment related by the study author.
No changes in body weight and body weight gains were observed with any of the test groups.
There were no treatment related effects at any exposure level on reproductive indices, time of mating, gestational length, post-implantation loss, pup survival or pup sex ratio.

Effects on Foetus

The pup survival index was lower in the low and mid dose groups on postnatal day 4 with 97.1 and 93.0% respectively when compared to control with 99.4% survival. The differences were considered unrelated to the test substance by the study author due to the lack of a decrease in the high dose group.
No treatment-related effects on pup body weight and size at any dose levels were observed.

Remarks - Results

Gavage administration of test substance at dose levels up to, and including, 150 mg/kg bw/day produced no indication of reproductive toxicity at any dose level. There were no effects on prenatal/early neonatal growth and survival of the offspring.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day, the highest dose tested in this study conducted using Crl:CD(SD) strain rats, based on the absence of adverse effects at this dose.

TEST FACILITY TERC (2009a)

B.9. Prenatal developmental toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 414 Prenatal Developmental Toxicity
Species/Strain Rats/Crl:CD(SD)
Route of Administration Oral – gavage
Exposure Information Exposure days: 14 days (from implantation to gestational day 20)
Vehicle Propylene glycol

Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	24 female	0	0
Low dose	24 female	15	0
Mid dose	24 female	60	0
High dose	24 female	150	0

Mortality and Time to Death
All test animals survived the study period.

Effects on Dams
Body weight gains in animals from mid and high dose groups for gestation day 6 to 9 was decreased by 33.6% and 50.4% respectively. Feed consumption was also reduced in these group ranging from 8.6 to 19.1% from gestational day 6 to 9 and 9 to 12. Body weight gain and feed consumption were similar to controls for the remainder of the study.

No treatment related effects on organ weights, pregnancy rates, resorption rates, litter size, numbers of corpora lutea or implantations, percent pre-implantation loss, percent post-implantation loss, foetal sex ratios, foetal body weight or gravid uterine weights and gross pathological changes were observed with any treatment group.

Effects on Foetus
One foetus and one litter from the low dose group exhibited forelimb flexture and one foetus and one litter from the same dose group showed hydrocephaly and dilated perinasal area. The observations occurred at low frequencies and lacked a dose-response relationship and were considered by the study author to not be related to the test substance.

A single foetus from high dose group had ventricular septal defect, ventricular double outlet and situs inversus. It was considered not related to treatment by the study author due to an isolated case.

Skeletal examination showed delayed ossification of frontal, interparietal, parietal, occipital, sternebrae and thoracic centra and class I & II wavy ribs, calloused ribs and extra first lumbar rib in different foetuses/litters from different groups. The finding lacked a dose-response relationship and the occurrence frequencies were low and hence were considered to be not test substance related by the study author.

Remarks – Results
Administration of the test substance by oral gavage at dose levels up to and including 150 mg/kg bw/day during pregnancy produced no treatment-related developmental toxicity in Crl:CD(SD) rats.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) for developmental toxicity was established as 150 mg/kg bw/day, the highest dose tested in this study, based on the absence of adverse effects seen at this dose.
The NOEL for maternal toxicity was established as 15 mg/kg bw/day based on the decrease in weight gain and feed consumption seen at higher doses of 60mg/kg bw/day and 150 mg/kg bw/day.

TEST FACILITY TERC (2012)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Pre incubation procedure
Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA
Metabolic Activation System S9 fraction from Aroclor™ induced rat liver
Concentration Range in a) With metabolic activation: 10–5000 µg/plate

Main Test	b) Without metabolic activation: 10–5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 3330	≥ 2500	> 5000	Negative
Test 2		≥ 2500	> 5000	Negative
Present				
Test 1	≥ 5000	≥ 5000	> 5000	Negative
Test 2		≥ 5000	> 5000	Negative

Remarks - Results	No significant increase in the frequency of revertant colonies were recorded for the bacterial strains, with any dose, either with or without metabolic activation. The positive controls produced satisfactory responses, thus confirming the activity of S9-mix and the sensitivity of the bacterial strain.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Covance (2007)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Rat/CD ISG
Cell Type	Lymphocytes
Metabolic Activation System	S-9 fraction from Aroclor 1254 induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	23, 45, 91, 182, 363*, 726*, 1452*	4 h	24 h
Test 2	11, 23, 45, 91*, 182*, 363*, 726, 1452	24 h	24 h
Present			
Test 1	23, 45, 91, 182, 363*, 726*, 1452*	4 h	24 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				
Test 1	-	≥ 1452	> 1452	Negative
Test 2	-	≥ 363	> 1452	Negative
Present				
Test 1	-	> 1452	> 1452	Negative

Remarks - Results	The positive controls showed increased mutation frequency, confirming the validity of the test system. The mutation frequencies in the test groups

did not show a biologically relevant increase, compared to controls. The test substance was toxic to the cells at highest concentration (1452 µg/ml media) with an exposure period of 4 h and at the 3 highest concentrations (363, 726 and 1452 µg/ml) with an exposure period of 24 h without metabolic activation as determined by relative mitotic index.

CONCLUSION The notified chemical was not clastogenic to rat lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY TERC (2007c)

B.12. Genotoxicity – in vivo

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain Mice/Crl:CD-1(ICR)
Route of Administration Oral – gavage
Vehicle Propylene glycol
Remarks - Method No significant protocol deviations. The test substance was administered on 2 consecutive days where as the positive control was administered only once.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Blood Collection Time hours*
I (vehicle control)		0	48 h
II (low dose)	6M	150	48 h
III (mid dose)	6M	300	48 h
IV (high dose)	6M	600	48 h
V (positive control, CP)	6M	40	48 h

CP=cyclophosphamide

RESULTS
Doses Producing Toxicity During the range finding study doses of 750, 1,000 and 2,000 mg/kg bw lead to deaths. During the main study one male animal from the 300 mg/kg bw dose group had a decrease in body weight and clinical observations of perioral soiling, noisy and laboured respiration. One animal from the 600 mg/kg bw dose group showed treatment related clinical signs including uncoordinated gait, muscle tremors and slow respiration.
Genotoxic Effects The test substance is considered negative in this micronucleus assay. The test substance did not induce a statistically significant increase in the frequency of micronucleated reticulocytes over the levels observed in the vehicle control.
Remarks - Results The positive control group had significantly increased frequencies of micronucleated reticulocytes compared to vehicle treated group.

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

TEST FACILITY TERC (2009b)

B.13. Dermal absorption – in vitro

TEST SUBSTANCE Notified Chemical (pH adjusted to 9.8 using concentrated HCl)

METHOD OECD TG 428 Skin Absorption: in vitro Method.
Remarks - Method No significant protocol deviations. The test substance was ^{14}C-labelled at position 4 ([4-^{14}C] 3-amino-4-octanol). The test substance was diluted in distilled water and the pH adjusted to around 8.5 using hydrochloric acid and the

	absorption was measured in human skin, in vitro using a flow-through cell system. The test substance was applied at two concentrations 0.5% and 10% (w/v) on 6 different skin sections each. The exposure period was 24 h and regular samples were collected at different time intervals (1, 2, 4, 6, 8, 10, 12, 16, 20 & 24 h) for analysis to estimate rate of absorption of the test substance. Following the last sample and surface wash, each chamber was tape-stripped with 15 sequential strips that were combined and used for analysis.
RESULTS	Total penetration through skin was 51.4 ± 8.9% and 20.6 ± 10.3 % for 0.5% and 10% test substance concentrations respectively. Total recovery of test substance was 98.5 ± 7.9% and 105.8 ± 8.7% for 0.5% and 10% concentration respectively.
Remarks - Results	The integrity of the skin was tested using tritiated water and was within the acceptability criteria.
CONCLUSION	The test substance showed absorption through the skin, which was higher at lower concentration of 0.5% than that of higher concentration of 10%.
TEST FACILITY	Notox (2009)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD) Method
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Notified chemical		*Reference substance (Aniline)*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0.3	1	-0.4
7	32.5	8	60.0
12	61.8	12	75.5
21	99.2	21	95.6
28	105.5	28	107.9

Remarks - Results	All validity criteria for the test were satisfied. The reference compound, Analine, reached the 60% pass level by day 8 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the Notified polymer after the cultivation period was 105.5% and it reached the pass level within the 10-day window. Therefore, the test substance is classified as readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	TERC (2007c)

C.2. Ecotoxicological Investigations

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Static Test
Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	Not reported
Water Hardness	144 mg $CaCO_3$/L
Analytical Monitoring	HPLC/MS Analysis
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Cumulative mortality (%)*				
Nominal	*Mean measured*		*4.5 h*	*24 h*	*48 h*	*72 h*	*96 h*

Control	Control	*20*	*0*	*0*	*0*	*0*	*0*
6.3	*6.8*	*20*	*0*	*0*	*0*	*0*	*0*
13	*14*	*20*	*0*	*0*	*0*	*0*	*0*
25	*27*	*20*	*0*	*0*	*0*	*0*	*0*
50	*52*	*20*	*5*	*5*	*5*	*5*	*5*
100	*96*	*20*	*75*	*100*	*100*	*100*	*100*

LC50 68 (52 – 96) mg/L at 96 hours
NOEC 27 mg/L at 96 hours.
Remarks – Results The actual concentrations of the test substance were measured periodically at 0, 48, and 96 hours within the 96-h test period. Therefore, median lethal concentration (LC50) and no observed effect concentration (NOEC) were calculated based on the mean measured concentrations of the test substance.

All validity criteria for the test were satisfied. All the exposure treatments were observed to be clear and colourless. The 96-hour LC50 and the confidence interval were calculated by probit analysis, the moving average method, and binomial probability with nonlinear interpolation method.

CONCLUSION The notified chemical is harmful to fish

TEST FACILITY Wildlife (2007a)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – Static Test
Species Zebra Fish (*Brachydanio rerio*)
Exposure Period 96 hours
Auxiliary Solvent Not reported
Water Hardness 144 mg $CaCO_3$/L
Analytical Monitoring Total Organic Carbon (TOC) Analysis
Remarks – Method The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration (mg/L)	*Number of Fish*	*Cumulative mortality (%)*				
		3 h	*24 h*	*48 h*	*72 h*	*96 h*
Control	*7*	*0*	*0*	*0*	*0*	*0*
100	*7*	*0*	*0*	*0*	*0*	*0*

LC50 > 100 mg/L at 96 hours
NOEC 100 mg/L at 96 hours.
Remarks – Results All validity criteria for the test were satisfied. The concentrations of the test substance were determined by measuring TOC analyses periodically at 0, 48, and 96 hours within the 96-h test period. The test was conducted as a limit test. The LC50 and NOEC values were determined based on visual observations.

CONCLUSION The notified chemical is not harmful to fish

TEST FACILITY Supervision (2010)

C.2.1. Chronic toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 204 Fish, Prolonged Toxicity Test: 14-day study - static-renewal.
Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	14 days
Auxiliary Solvent	Not reported
Water Hardness	144 mg $CaCO_3$/L
Analytical Monitoring	HPLC/MS Analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

Results

Concentration (mg/L)		*Number of Fish*	*Cumulative mortality (%)*												
			Day												
Nominal	*Mean measured*		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
Control	Control	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
6.3	*6.3*	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
13	*13*	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
25	*25*	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
50	*50*	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
100	*103*	*20*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*

Mean measured Concentration (mg/L)	Mean Total Length ±SD (mm)	Mean Wet Weight ±SD (g)
Control	52.4 ± 3.2	1.3 ± 0.253
6.3	52.4 ± 3.06	1.3 ± 0.233
13	52.4 ± 3.63	1.31 ± 0.267
25	52.1 ± 3.41	1.36 ± 0.281
50	52.2 ± 4.05	1.32 ± 0.258
103	52.4 ± 2.95	1.28 ± 0.280

Threshold level of lethal effect	>103 mg/L (14 days)
Threshold level of observed effect (sublethal)	>103 mg/L (14 days)
NOEC	>103 (14 days)

Remarks – Results

All validity criteria for the test were satisfied. Test solutions were renewed every 3-4 days. The actual concentrations of the test substance were measured at the beginning and at the beginning and end of each renewal cycle during the test. Therefore, the test endpoints were calculated based on the mean measured concentrations of the test substance. No statistically significant effect was observed for mean lengths and wet weights of the test species exposed to the test substance for 14 days. The test species exposed to the test substance at the concentration < 103 mg/L appeared normal with no mortality, overt signs of toxicity or impact on growth.

All the exposure treatments were observed to be clear and colourless. The Toxstat statistical software was used to calculated the endpoint values.

CONCLUSION The notified chemical is not harmful to fish on a chronic basis

TEST FACILITY Wildlife (2011)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None reported
Water Hardness 128 mg $CaCO_3$/L
Analytical Monitoring HPLC/MS Analysis
Remarks - Method The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Cumulative % Immobilised*	
Nominal	*Mean measured*		*24 h*	*48 h*
Control	*Control*	*20*	*0*	*0*
6.3	*6.5*	*20*	*0*	*0*
13	*13*	*20*	*0*	*0*
25	*25*	*20*	*0*	*0*
50	*49*	*20*	*0*	*65*
100	*98*	*20*	*5*	*100*
200	*193*	*20*	*95*	*100*

EC50 44 (25 – 98) mg/L at 48 hours
NOEC 13 mg/L at 48 hours
Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the test substance were measured at 0 and 48 hours. Therefore, median lethal concentration (EC50) and no observed effect concentration (NOEC) were calculated based on the mean measured concentrations of the test substance.

All the exposure treatments were observed to be clear and colourless. The 48 hour EC50 and the confidence interval were calculated by probit analysis, nonlinear interpolation and binomial probability methods.

CONCLUSION The notified chemical is harmful to aquatic invertebrates

TEST FACILITY Wildlife (2007b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
Species *Pseudokirchneriella subcapitata*
Exposure Period 96 hours
Concentration Range Nominal: 0.24, 0.81, 2.7, 9.0, 30, and 100 mg/L
Auxiliary Solvent Not reported
Water Hardness Not reported
Analytical Monitoring HPLC/MS Analysis
Remarks - Method The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Biomass (72 h)		*Growth (72 h)*	
E_yL50 (mg/L)	*NOE_yL (mg/L)*	*E_rL50 (mg/L)*	*NOE_rL (mg/L)*
4.7 (3.6 – 6.0)	< 0.24	39 (35 – 44)	0.81

Remarks - Results

All validity criteria for the test were satisfied. The actual concentrations of the test substance were measured at 0 and 69 hours. The recovery rate was > 95% for all the treatments. Therefore, median lethal concentration (EC50) and no observed effect concentration (NOEC) were calculated based on the nominal concentrations of the test substance.

All the exposure treatments were observed to be clear and colourless. The EC50 values were calculated using nonlinear regression method. The test was conducted for 96 hours but standard 72-hr test endpoints were presented.

CONCLUSION

The notified chemical is harmful to algae

TEST FACILITY

Wildlife (2007c)

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