File No.: STD/1728

November 2020

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

Octanoic acid, 2-butyl

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019* (the IC Act) and *Industrial Chemicals (General) Rules 2019* (the IC Rules) by following the *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019* (the Transitional Act) and *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019* (the Transitional Rules). The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is administered by the Department of Health, and conducts the risk assessment for human health. The assessment of environmental risk is conducted by the Department of Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the AICIS website. For enquiries please contact AICIS at:

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Executive Director
AICIS

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SUMMARY

The following details will be published on our website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1728	Cintox Australia Pty Ltd	Octanoic acid, 2-butyl	ND	≤ 200 tonnes per annum	Additive for mining/metal extraction and metalworking fluids

ND = Not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information, the assessed chemical cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

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 Aquatic Toxicity (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 settings described, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

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

Environmental Risk Assessment
On the basis of the PEC/PNEC ratio, the assessed chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

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 assessed chemical, during reformulation:
  - Enclosed/automated processes if possible
  - Local exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the assessed chemical during reformulation:
  - Avoid contact with skin and eyes

- 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 assessed chemical [as introduced, during reformulation or during final use]:
  - Impervious gloves
  - Protective clothing
  - Respiratory protection if inhalation is expected

  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 assessed 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.

Emergency procedures

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

Disposal

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

Regulatory Obligations

Specific Requirements to Provide Information
This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under section 101 of the IC Act the introducer of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if:

- the function or use of the chemical has changed from an additive for mining/metal extraction and metalworking 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 on the skin sensitisation of the assessed chemical;
- additional information has become available to the person as to an adverse effect of the chemical on human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

Safety Data Sheet
The SDS of product containing the assessed chemical provided by the applicant was reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND APPLICATION DETAILS

APPLICANT(S)
Cintox Australia Pty Ltd (ABN: 63 122 874 613)
26 Male Street
BRIGHTON VIC 3186

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

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
Data items and details exempt from publication include: analytical data, degree of purity, impurities, import volume and identity of analogue chemicals.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are varied for adsorption/desorption, dissociation constant, flammability, explosive properties, and oxidising properties.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
EU (2017)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Isocarb 12

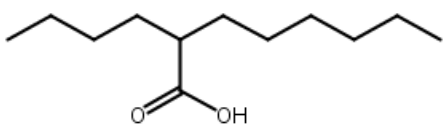
CAS NUMBER
27610-92-0

CHEMICAL NAME
Octanoic acid, 2-butyl-

OTHER NAME(S)
2-Butyloctanoic acid
α-Butylcaprylic acid

MOLECULAR FORMULA
$C_{12}H_{24}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
200.3 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: viscous yellowish liquid

Property	*Value*	*Data Source/Justification*
Pour Point	-75 °C at 102.3 kPa	Measured
Boiling Point	283 °C at 101.1 kPa	Measured
Relative Density	887.6 kg/m^3 at 20°C	Measured
Vapour Pressure	7.2 × 10^{-6} kPa at 20 °C	Measured and calculated
Water Solubility	2.2 ×10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable function groups
Partition Coefficient (n-octanol/water)	log Pow = 2.38 at 25 °C; log Pow = 4.33 at 25 °C	Measured
Surface tension	71.8 mN/m at 20°C	Measured
Adsorption/Desorption	log K_{oc} = 2.48	Calculated by Epi Suite KOCWIN (USEPA, 2012)
Dissociation Constant	4.82 ± 0.40	Calculated
Flash Point	154°C at 100 kPa	Measured
Autoignition Temperature	223 °C at 101.8 kPa	Measured
Explosive Properties	Not expected to be explosive	Contains no functional groups that imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that imply oxidising properties
Viscosity	27.3 mPa s (dynamic)	Measured

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

Reactivity
The assessed 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 assessed 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 ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS
The assessed chemical will not be manufactured in Australia. It will be imported at 100% concentration into Australia.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	100-200	100-200	100-200	100-200	100-200

PORT OF ENTRY
Major ports in Australia

IDENTITY OF MANUFACTURER/RECIPIENTS
Cintox Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The assessed chemical will be imported in neat form in sealed 205 L drums. It will be reformulated into end-use products in various types of containers at up to 10% concentration and expected to be transported by road.

USE
The assessed chemical will be used as a dispersing additive in metalworking fluids and as an additive in mining/metal extraction industry for solvent extraction process.

OPERATION DESCRIPTION
The assessed chemical will not be manufactured in Australia. The imported assessed chemical will be reformulated into end-use industrial products at up to 10% concentration.

Reformulation
During reformulation, the imported chemical will be transferred from the containers into the blending vessels using automated pumping/dosing equipment. Operators will open the sealed containers containing the assessed chemical and connect them to the blend vessels by pipes/hoses using quick connect fittings. The blending vessels will be sealed, in a bunded area, and supplied with local fume extraction. Quality assurance (QA) staff will take samples for analysis from the finished metal working products containing up to 10% assessed chemical. The formulated products will be gravity fed to an automated filling machine and filled into 205 L drums or 5 L plastic bottles.

End-use
Mining /Metal Extraction
At the metal extraction site, the neat assessed chemical will be pumped from the imported bunded containers into holding tanks. Metered quantities of the assessed chemical will then be pumped from the tanks into the solvent extraction closed-loop water recirculation circuit. This is to facilitate the transfer of the metal between the aqueous and organic phases. This process will be followed by precipitation and filtration of the metal salt. The solvent extraction unit will contain the collected metal and most of the assessed chemical which will go into the smelting process. The remaining raffinate will contain a small amount of the assessed chemical and will be neutralised, dewatered, thickened and formed into a solid filtercake and disposed of back into the mine pit. The mineral extraction will be an automated process with continuous water/fluid recirculation.

Metalworking Fluids/Lubricants
The formulated metalworking fluids containing 10% of the assessed chemical will be further diluted 1:10 prior to use in metal forming mill and lathe unit operations. The diluted metalworking fluid will be coated onto the metal surface and excess fluid will drip down into a sump and then recirculated within the equipment after filtering process. Residual fluid will be removed from the metal part using a high velocity air blast. These operations will be conducted within enclosed machinery supplied with local ventilation to remove any mists and vapours of the fluid. However, there will be a manual occasional top ups of the fluids poured into the machinery reservoir.

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 warehousing	4	30
Blending plant operators and Maintenance	5	12
Blending QA staff	2	12
Metalworking Operators	8	200
Metal Extraction End-use Plant operators	4-12	200

EXPOSURE DETAILS

Transport and warehousing
Transport and storage workers may come into contact with the assessed chemical at ≤ 100% concentration only in the unlikely event of a spill or accidental rupture of containers.

Reformulation
Dermal, ocular and inhalation exposure of workers to the assessed chemical at ≤ 100% concentration may occur during the blending, filling, and quality control analysis operations, and during cleaning and maintenance of equipment processes. The blending facilities will be well ventilated, with control systems for accidental spills and wastewater treatment. Workers will wear personal protective equipment such as gloves, eye protection, protective clothing and hard hats. QA staff will wear laboratory coat, safety glasses, and impervious gloves. Cleaning and maintenance workers will wear overalls, safety glasses and hard hats.

End-use
Mining /Metal Extraction
End users may be exposed to the assessed chemical at a concentrations of ≤ 100% during mining/metal extraction operations mainly during transfer operation of the assessed chemical. Exposure of workers to the assessed chemical will be mitigated by the use of enclosed and automated systems. The operation facilities will be well ventilated and workers will wear personal protective equipment to further minimise exposure.

Metalworking Fluids/Lubricants
End users may be exposed to the assessed chemical at a concentrations up to 10% during metalworking fluids/lubricants operations. Worker exposure may occur during the transfer of finished metalworking products from the storage containers into the machinery reservoirs and during cleaning of equipment and maintenance. Dermal, ocular and inhalation exposure to the assessed chemical will be reduced by the use of enclosed processes, and/or engineering controls such as shielding and local ventilation. In addition, workers will wear personal protective equipment to further reduce exposure.

6.1.2. Public Exposure
The assessed chemical and products containing it will not be available to the public. The public will not come into contact with surfaces treated with metalworking fluids containing the assessed chemical. The public will not have access to metal extraction site where the assessed chemical will be used. Therefore, public exposure to the assessed chemical is not expected to occur.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the assessed chemical and an analogue chemical are summarised in the following table. For details of the studies, refer to Appendix B. The analogue chemical was considered to have similar toxicity profile to the assessed chemical due to the similarity of the structure and identical functional group presented in these chemicals.

Endpoint	***Test Substance***	***Result and Assessment Conclusion***
Acute oral toxicity – rat (OECD 423)	Assessed chemical	LD50 > 2,000 mg/kg bw; low toxicity
Acute oral toxicity – rat (OECD 401)	Assessed chemical	LD50 > 2,000 mg/kg bw; low toxicity in male rats (n = 5); LD50 = 1358 mg/kg bw; harmful in female rats (n = 20)
Acute dermal toxicity – rat	Analogue chemical	LD50 > 2,000 mg/kg bw; low toxicity
Skin irritation – rabbit (OECD TG 404)	Assessed chemical	slightly irritating
Eye irritation – rabbit (OECD TG 405)	Assessed chemical	slightly irritating
Skin sensitisation – mouse local lymph node assay (OECD TG 429)	Assessed chemical	Evidence of sensitisation at 50% concentration
Skin sensitisation – mouse local lymph node assay (OECD TG 429)	Assessed chemical	No evidence of sensitisation up to 50%
Repeat dose oral toxicity – rat, 28 days	Analogue chemical	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	Assessed chemical	non mutagenic

Endpoint	*Test Substance*	*Result and Assessment Conclusion*
Genotoxicity – *in vitro* Mammalian Cell Gene Mutation Test - L5178Y mouse lymphoma cells	Analogue chemical	non genotoxic
Genotoxicity – *in vivo* Chromosome aberration in Chinese hamster V79 cells	Analogue chemical	non genotoxic
Reproductive and developmental toxicity – rat	Assessed chemical	maternal toxicity NOAEL = 25 mg/kg bw/day foetal toxicity NOAEL = 200 mg/kg bw/day

Toxicokinetics, Metabolism and Distribution
No toxicokinetic data on the assessed chemical were submitted. Based on the low molecular weight of the assessed chemical (200.3 g/mol), there is potential for the chemical to cross biological membranes. However, the low water solubility (2.2×10^{-3} g/L at 20 °C) and partition coefficient (log Pow 2.38 at 25 °C; 4.33 at 25 °C) of the assessed chemical indicate limited potential for dermal absorption.

Acute Toxicity
The assessed chemical is of low acute oral toxicity in male rats in two studies (OECD TG 401 and 423), but harmful in female rats in the second study (OECD TG 401). There were 4/5 female rat deaths at 1,300 mg/kg bw and 2/5 female rat deaths at 2,020 mg/kg bw in the second study.

The assessed chemical is also of low acute dermal toxicity based on analogue data in rats. No acute inhalation toxicity data on the assessed chemical was submitted.

Irritation
The assessed chemical is slightly irritating to skin (OECD TG 404) and eyes (OECD TG 405) based on tests conducted in rabbits.

Sensitisation
There were two Local Lymph Node Assays (LLNA) conducted for the assessed chemical in 2003 and 2004 using the OECD TG 429. No protocol deviations were reported in both studies.

In the first LLNA study, the Stimulation Index (SI) was reported as 1.6 at 25% concentration and 5.8 at 50% concentration. At 100% concentration one female animal died (on day 3) and other 3 female animals were terminated due to adverse body weight effects and clinical signs.

In the second LLNA study (conducted in 2004 by a different laboratory), the SI values were 1.0, 2.6, 1.7 and 1.9 at 10, 25, 50 and 50% concentrations, respectively, reporting the chemical was not a skin sensitiser.

Based on the conflicting results of the two LLNA studies, the assessed chemical is not classified as a skin sensitiser. However, the skin sensitisation potential of the assessed chemical could not be ruled out, based on the results of the first LLNA.

Repeated Dose Toxicity
In a repeated dose oral (gavage) toxicity study (OECD TG 407), the analogue chemical was administered to rats at doses 0, 50, 250, and 1,000 mg/kg bw/day for 28 days with two weeks post-exposure recovery period.

All animals including the recovery animals survived the scheduled treatment. There were no significant adverse treatment related effects observed in any of the systemic parameters measured. However, there were weight reductions of organs due to body weight gain reductions in males. The No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established as 1,000 mg/kg bw/day.

Mutagenicity/Genotoxicity
The assessed chemical was not mutagenic in a bacterial reverse mutation test. The analogue chemical was not mutagenic in an *in vitro* mammalian cell gene mutation test and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Developmental Toxicity
In a developmental toxicity study (non-guideline study), mated female rats (25 per dose group) were dosed daily from day 6 to day 19 of gestation by oral gavage doses of the assessed chemical at 0, 25, 200 or 400 mg/kg bw/day. Maternal toxicity was observed at 400 mg/kg bw/day in all animals and four animals of this dose group had to be discontinued and 2 of them had to be killed prematurely for animal welfare reasons. At 200 mg/kg bw/day maternal toxicity was limited to clinical observations. No maternal toxicity was observed at the low dose group. The dose group of 400 mg/kg bw showed lower mean foetal weight, and an increased incidence of supernumerary ribs. Foetal ossification at the high dose group was slightly reduced. No obvious foetal effects were noted at 25 and 200 mg/kg bw/day and the foetal effects at the high dose group occurred with maternal toxicity. The No Observed Adverse Effect Level (NOAEL) was established as 200 mg/kg bw/day for foetal toxicity and 25 mg/kg bw/day for maternal toxicity in this study.

Health Hazard Classification
Based on the available information, the assessed chemical cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia. Skin sensitisation cannot be ruled out based on conflicting results reported in the two studies (conducted in two different laboratories using the same OECD TG 429).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The assessed chemical is a slight skin and eye irritant. The skin sensitisation potential for the assessed chemical could not be ruled out based on the studies provided with up to 50% concentration tested.

During reformulation and end use (mining /metal extraction and metalworking fluids/lubricants), workers may be at risk of slight skin and eye irritation effects of the assessed chemical. However, the risk will be reduced through the control measures in place to minimise worker exposure, including the use of automated processes and use of PPE (such as protective clothing, safety glasses and gloves).

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

6.3.2. Public Health
The assessed chemical and products containing it will not be sold or available to the public. Public exposure to the assessed chemical is not expected to occur.

When used in the proposed manner, the assessed 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 assessed chemical is imported for reformulation into finished industrial products for use as a metal working fluids and as an additive for mining/metal extraction solvent. During any formulation and mixing, release of the assessed chemical to the environment is expected to be negligible as these processes occur in closed systems in industrial settings. Empty import drums containing residues of the assessed chemical (1% of the total import volume) are expected to be cleaned, with the residual waste sent to on-site wastewater treatment facilities. Any accidental spills are to be collected and disposed of in accordance with local government regulations. Wash waters from equipment cleaning, containing the assessed chemical are expected to be collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
The assessed chemical will be used as a metal working fluid and as an additive in mining/metal extraction industry. The finished metal working fluids containing the assessed chemical will be used at industrial sites. Release from spills are expected to be very limited. The diluted metal working fluid will be circulated through contained systems until they are spent.

As a metal extraction additive the assessed chemical will be added to the solvent extraction circuit which is a closed-loop water recirculation circuit. Release from spills are expected to be limited, with less than 2% of the import volume, as estimated by the applicant. Most of the assessed chemical will chelate the metal extracted and will be combusted during subsequent metal smelting. Residual amounts of the assessed chemical will end up in solid residues/wastes.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the assessed chemical is expected to remain as residues in empty product containers. These containers are expected to be either recycled or disposed of to landfill. The disposal of spent metalworking fluids containing the assessed chemical is expected to be by use as low grade burner fuel or to landfill. Residual assessed chemical in residues/wastes from mining/metal extraction will be disposed of to the mine pit.

7.1.2. Environmental Fate

The assessed chemical is expected to be readily biodegradable (73% biodegradation after 28 days). For the details of the environmental fate studies refer to Appendix C. The half-life of the assessed chemical in air is calculated to be < 9.3 h, based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). Therefore, the assessed chemical is not expected to persist in the air compartment.

The majority of assessed chemical is expected to be combusted during smelting or use as low grade fuels during disposal or degrade in landfill. A small amount (1%) is expected to be released from industrial sites and will be treated on-site before release to sewer.

During treatment, most of the assessed chemical is expected to be removed given it is readily biodegradable. The assessed chemical may have a potential for bioaccumulation based on its measured partition coefficient (log Pow = 2.38 – 4.33), however, this is likely to be limited due to its ready biodegradability. Sludge from wastewater treatment plants which may contain a limited amount of the assessed chemical is expected to be disposed of to landfill or applied to agricultural soils.

The assessed chemical in landfill or soil is expected to be moderately mobile based on its estimated soil adsorption coefficient (log Koc = 2.48). However, in landfill, soil and water, the assessed chemical is expected to readily degrade into water, and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in a portion of the assessed chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 1% release of the assessed chemical into sewer systems nationwide over 260 working days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes based on the properties of the assessed chemical has not been considered for this scenario, and therefore no removal of the assessed chemical during sewage treatment processes, is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import Volume	200,000	kg/year
Proportion expected to be released to sewer	1%	
Annual quantity of chemical released to sewer	2,000.000	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	7.69	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC - River:	1.58	µg/L
PEC - Ocean:	0.16	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m^2/year (10 ML/ha/year). The assessed chemical in this volume is assumed to infiltrate and

accumulate in the top 10 cm of soil (density 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 1.577 µg/L may potentially result in a soil concentration of approximately 10.5 µg/kg. Accumulation between applications is not expected as the assessed chemical readily degrades.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h EC50 = 13 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 31 mg/L	Harmful to daphnids
Algal Toxicity	72 h ErC50 = 13 mg/L 72 h NOEC = 1.3 mg/L	Harmful to algae
Toxicity to soil microorganisms	28 d EC50 = 828 mg/kg	Slightly toxic to soil microorganisms
Terrestrial plants toxicity	21 d EC50 = 133 mg/kg dry weight	Not harmful to terrestrial plants
Earthworms Toxicity	56 d EC50 > 120 mg/kg soil	Slightly toxic to earthworms

Based on the above ecotoxicological endpoints, the assessed chemical is expected to be acutely harmful to aquatic life.

The assessed chemical is rapidly degradable. The two partition coefficient studies provided were conflicting regarding the chemical's potential to bioaccumulate. However, based on supporting evidence provided by the applicant, the assessed chemical is not considered to be bioaccumulative. One chronic endpoint is available. Therefore, the aquatic chronic hazard is determined using both the chronic and acute data and the most stringent outcome is adopted. When the chronic hazard is determined based on the lowest acute endpoint, taking into account the substance is rapidly degradable and not potentially bioaccumulative, the result is: "Not classified for long-term hazard". When the chronic hazard is determined based on the lowest chronic endpoint, taking into account the substance is rapidly degradable the result is: "Not classified for long-term hazard". Both methods gave the same outcome. Therefore the overall chronic classification is: "Not classified for long-term hazard".

Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the assessed chemical is formally classified as "Acute Category 3 (H402): Harmful to aquatic life".

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the assessed 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 assessed chemical. Three acute ecotoxicity endpoints for aquatic species from three trophic levels are available but one endpoint value is modelled data. Therefore, an assessment factor of 250 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment			
72 h ErC50 (Algae).	13		mg/L
Assessment Factor	250		
Mitigation Factor		1.00	
PNEC:	52		µg/L

The Predicted No-Effect Concentration (PNEC) was also calculated based on the most sensitive terrestrial species (LC50 earthworm) and an assessment factor of 100 as there is data for three endpoints.

Predicted No-Effect Concentration (PNEC) for the Terrestrial Compartment			
Soil microorganisms EC50	120		mg/kg
Assessment Factor	100		
Mitigation Factor		1.00	
PNEC	1,200		µg/kg

7.3. Environmental Risk Assessment

The Risk Quotient for the aquatic environment (Q = PEC/PNEC) was calculated based on the PEC and PNEC.

Risk Assessment	PEC (µg /L)	PNEC (µg /L)	Q
Q - River:	1.58	52	0.030
Q - Ocean:	0.16	52	0.003

The Risk Quotients (Q = PEC/PNEC) for the worst case scenario have been calculated to be < 1 for the river and ocean compartments. Although some of the assessed chemical may be released into waterways, it is not expected to reach ecotoxicologically significant concentrations. The assessed chemical is expected to rapidly degrade in the environment and therefore bioaccumulation is not expected.

The Risk Quotient (Q = PEC/PNEC) for the terrestrial environment was calculated as follows.

Risk Assessment	PEC (µg/kg)	PNEC (µg/kg)	Q
Q – soil	10.5	1,200	0.009

Therefore on the basis of the aquatic and the terrestrial PEC/PNEC ratios, the assessed chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -75 °C at 102.3 kPa

Method	ASTM D 97-66
Remarks	Pour point was measured.
Test Facility	SASOL (2014a)

Boiling Point 283 °C at 101.1 kPa

Method	ASTM D 1120
Remarks	Ebilliometer method was used.
Test Facility	SASOL (2014b)

Relative Density 887.6 kg/m^3 at 20°C

Method	ASTM D 7042
Remarks	Stabinger viscosimeter method was used.
Test Facility	SASOL (2014c)

Vapour Pressure 7.2×10^{-6} kPa at 20 °C (calculated)
3.1×10^{-4} at 50 ºC (calculated)

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	A dynamic method with an ebulliometer was used.
Test Facility	LTP (2015)

Water Solubility 2.2×10^{-3} g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Flask Method
Test Facility	Chelab (2015a)

Partition Coefficient (n-octanol/water) (Study #1) log Pow = 2.38 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method
Test Facility	Chelab (2014)

Partition Coefficient (n-octanol/water) (Study #2) log Pow = 4.33 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method
Test Facility	Chelab (2015b)

Surface Tension 71.8 mN/m at 20 °C

Method	ISO 304 (1985)
Remarks	Du Nouy ring method was used. Concentration at 2.2 mg/L.
Test Facility	SASOL (2016)

Flash Point 154 °C at 100 kPa

Method	ISO 2592
Remarks	Open cup method was used.
Test Facility	SASOL (2014d)

Autoignition Temperature 223 °C at 101.8 kPa

Method	DIN 51794 (Liquid and Gas)
Test Facility	SASOL (2014e)

Explosive Properties Not expected to be explosive

Method	RIP A Explosive properties
Remarks	The chemical shows no chemical groups associated with explosive properties.
Test Facility	SASOL (2014f)

Viscosity 27.3 mPa s (dynamic) at 20 °C

Method	ASTM D 7042
Remarks	Stabinger viscometer method was used.
Test Facility	SASOL (2014g)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (1996)
Species/Strain	Rat/Sprague Dawley SD
Vehicle	Water
Remarks – Method	No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 per sex	2,000	0/6

LD50	> 2,000 mg/kg bw
Signs of Toxicity	The following observations were noted after administration of the test substance: piloerection, hunched posture, salivation, reduced activity, swollen abdomen, difficulty in moving, hairloss on head and red staining on muzzle which were recovered by day 2 in females and by day 13 in males.
Effects in Organs	No abnormalities were noted on necropsy of animals.
Remarks – Results	The body weights were within the expected range.
CONCLUSION	The test substance is of low acute toxicity via the oral route.
TEST FACILITY	RTC (2000)

B.2. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 401 Acute Oral Toxicity (1981)
Species/Strain	Rat/HSD: Sprague-Dawley
Vehicle	None
Remarks – Method	No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 F	500	0/5
2	5 F	1,300	4/5
3	5 F	2,020	2/5
4	5 M	2,020	1/5
5	5 F	3,200	5/5

LD50	> 2,020 mg/kg bw in male rats = 1,358 mg/kg bw in female rats
Signs of Toxicity	The following observations were noted after administration of the substance: piloerection, activity decrease, polyuria, ptosis, respiratory gurgle, crust around nose and eyes, diarrhoea, nasal discharge, salivation and staining of muzzle which were recovered by day 8. Gasping and lateral recumbency were noted only in animals which died during the test.
Effects in Organs	No abnormalities were observed on necropsy of survived animals. One female in the 3,200 mg/kg group showed a ruptured oesophagus as from a dosing injury. Died animals showed matting or staining of muzzle, anal and genital areas and gas and discoloured contents in the gastrointestinal tract.
Remarks – Results	Body weights showed normal increase in surviving animals.

CONCLUSION	The test substance is of low acute toxicity via the oral route in male rats and harmful in female rats.
TEST FACILITY	Stillmeadow (1996)

B.3. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test (1987)
Species/Strain	Rat/Wistar Crl: WI(Han)
Vehicle	None
Remarks – Method	Minor deviations from the study plan, related to preparation of test substance and use of general and project staff, were not considered to have affected the outcome of the study.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity – Local	Desquamation was observed in 5 female and 4 males. Erythema (grade 1) was observed in 1 male and 1 female. Crust was observed in 2 females and scratches in 3 males and 3 females. Sign of irritation was not completely reversible within the observation period (14 days).
Signs of Toxicity – Systemic	No treatment related effects of systemic toxicity were observed.
Effects in Organs	No abnormalities were noted at the macroscopic examination.
Remarks – Results	Two females showed slight weight loss during the first week and all females had normal weight gain in the second week. All males showed normal weight gain. The effects on slight weight loss was considered secondary to the dressing by the study authors.
CONCLUSION	The test substance is of low acute toxicity via the dermal route.
TEST FACILITY	Erofins (2016)

B.4. Skin Irritation – Rabbit

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (1992)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 F
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks – Method	No protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.7	1.0	1.0	1	< 7 d	0
Oedema	0.0	0.0	0.0	0	0	0

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

Remarks – Results	No systemic effects related to treatment was observed. The body weights were within the expected range. Very slight erythema was observed at in all animals at 24 and 48 hour observation and in 2 animals at up to 72 hours and desquamation was observed after 7 days, however, all effects were reversible within 14 days.
CONCLUSION	The test substance is slightly irritating to the skin.
TEST FACILITY	RTC (2002a)

B.5. Eye Irritation – Rabbit

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (1987)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 F
Observation Period	4 days
Remarks – Method	No protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva – Redness	1.0	0.3	0.7	2	< 72 h	0
Conjunctiva – Chemosis	0.7	0.3	0.3	2	< 48 h	0
Conjunctiva – Discharge	0.7	0.3	0.3	2	< 48 h	0
Corneal Opacity	0.0	0.0	0.0	0	-	0
Iridial Inflammation	0.0	0.0	0.0	0	-	0

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

Remarks – Results	Slight to well defined conjunctival irritation (redness, chemosis and ocular discharge) was observed between 1 and 48 hours after treatment but was reversible within 72 hours. No significant body weight changes were observed. No systemic effects related to treatment were observed. The body weights were within the expected range.
CONCLUSION	The test substance is slightly irritating to eyes.
TEST FACILITY	RTC (2002b)

B.6. Skin Sensitisation – LLNA

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2002)
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone:olive oil (4:1 v/v)
Preliminary study	No
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using hexyl cinnamic aldehyde (HCA).
Remarks – Method	No protocol deviations.

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	299.5	N/A
25	4 F	475.1	1.6
50	4 F	1,730.4	5.8
100	4 F	-	-
Positive Control			
0	4 (sex unknown)	393.2	N/A
10	4 (sex unknown)	1,099.4	2.8
25	4 (sex unknown)	2,756.3	7.0
50	4 (sex unknown)	6,977.0	17.7

EC3 Not established in the study.

Remarks – Results One female animal dosed at 100% concentration died on day 3. The rest of the animals of this group were killed due to large bodyweight loss and poor clinical conditions such as thin appearance, greasy fur, hunched posture and reduced body temperature. All controls and all animals in low and mid dose groups showed greasy fur from day 1, and completely resolved by day 6 except the mid dose group.

All animals gained expected body weight during the study except for the high dose group animals that lost weight.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.

TEST FACILITY Huntingdon (2003)

B.7. Skin Sensitisation – LLNA

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2002)

Species/Strain Mouse/CBA/Ca

Vehicle Acetone:olive oil (4:1 v/v)

Preliminary study No

Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using hexyl cinnamic aldehyde (HCA).

Remarks – Method No protocol deviations.

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	6,251	1
10	4 F	6,421	1.0
25	4 F	16,234	2.6
50	4 F	10,757	1.7
50*	4 F	11,770	1.9
*Positive Control***			
0 (vehicle control)	5 F	1,255/1,606	1/1
10	5 F	2,894/3,119	2.3/1.9
20	5 F	6,930/6,982	5.5/4.3
40	5 F	9,418/18,853	7.5/11.7

*From a different batch

**Values measured in March 2003/May 2003

Remarks – Results	Clinical sign observations showed no adverse effects at any dose level during the study. Body weight gain of treated animals showed similar results to controls.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.
TEST FACILITY	Inveresk (2004)

B.8. Repeat Dose Oral Toxicity – Rats

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (2008)
Species/Strain	Rats/Wistar, Crl: WI(Han)
Route of Administration	Oral - Gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14-day
Vehicle	Corn oil
Remarks – Method	Minor deviations from the study plan, related to signing of report, were not considered to have affected the outcome of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5 per sex	0	0/10
Low Dose	5 per sex	50	0/10
Mid Dose	5 per sex	250	0/10
High Dose	5 per sex	1,000	0/10
Control Recovery	5 per sex	0	0/10
High Dose Recovery	5 per sex	1,000	0/10

Mortality and Time to Death

All animals including the recovery group animals survived the scheduled treatment.

Clinical Observations

Slight to severe salivation and moving the bedding were observed in some animals of the treatment groups and the recovery group. There were no ophthalmologic findings, changes or differences due to treatment in weekly clinical observations and effects on functional observation battery and body temperature.

Slightly lower mean body weight gain was observed in the high dose and recovery groups. Overall weight gain was statistically significantly lower in low, mid and high dose and recovery group males (-23.6%, -29.9%, 34.6% and -27% respectively, compared to the control mean). Such a great reduction was not observed in female groups (-9.1%, -7.1% and -9.5% respectively, in low, mid and recovery group, compared to the control mean). High dose females showed a mean weigh gain (up to 17.17% increase compared to the control group).

There were no statistically significant effects on food consumption in test groups except that a statistically significantly lower average daily food consumption was observed in the high dose female recovery group during the treatment and recovery period. Mean food consumption was in correlation with respective body weights.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no statistically significant or biologically relevant differences or test substance related toxicological effects for haematology or coagulation parameters and clinical biochemistry, except that there were statistically significantly lower mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelet count

(PLT), white blood cells (WBC) and higher monocytes values in the high dose male group compared with the controls, and not seen in high dose recovery males.

In males and females, all urinary parameters were normal except that there were slightly higher leukocyte levels in the urine of one male animal of high dose recovery group and two males of control recovery group.

Effects in Organs

The gross pathological observations, such as spots on epididymides, the spermatid granulomas of epididymis (high dose (4/5) and control recovery (2/5)) and the congestion in the ileum (control recovery 1/5) in males, the pelvic dilation of the kidney (control 1/5) and the cornual dilation of the uterus in (high dose 2/5) in females and enlarged mandibular lymph node in high dose group males (1/5) and 0/5 in the control recovery were reported. These were not considered to be adverse effects related to treatment as there were no histopathological changes.

In males at the end of the treatment period, absolute mean adrenals, thymus, thyroid/parathyroid weights in high dose (-19.5%, -38.1%, -54.9%) and absolute epididymides weights in low dose and high dose (-18.2, and -24.4%) were statistically significantly lower. Absolute mean spleen weights in mid dose group were statistically significantly lower (-24.4%). The relative mean (to brain weight) liver and kidney weights in low dose and mid dose, spleen weights in mid dose, thymus weights in mid dose and high dose, epididymides weights in all test groups and thyroid/parathyroid weights in low dose and high dose were statistically significantly lower (-11.5% and -12.2% for liver, -13% and -16.1% for kidney, -29.3% for spleen, -26.8% and -36.3% for thymus). A statistically significantly higher relative (to body weight) brain and testes weights in all dose groups (low, mid and high dose groups: 12.9%, 18.1%, and 12.1%; 12.7%, 10.9% and 11.5% respectively) and statistically significantly lower relative (to body weight) thymus and thyroid/parathyroid weights in high dose group were noted (-29.7% and -49.1% respectively).

In females at the end of treatment period, a statistically significantly higher absolute and relative (to body and brain weight) liver weight (28.1% and 32.9% respectively) was observed in the high dose group. There was statistically significantly lower absolute and relative (to body weight) thymus weights in high dose group (-38.7% and -36.3% respectively). A statistically significantly lower absolute and relative (to brain and body weight) thyroid/parathyroid weights in low dose (-35.5% and -33.6% respectively) and statistically significantly higher ovary weights relative to body weights were noted in high dose group (26.4% and 30.3% respectively).

There were no statistically or biologically significant effects on the absolute and relative organ weights in the animals at the end of the recovery period, except statistically significantly higher relative (to brain and body weight) ovary weights in high dose recovery females. As the effect was not observed in high dose females, it was not considered related to the treatment.

To the values having statistical significances, no histological correlate was observed for the increased or decreased weights. In the light of absence of adverse histopathological findings in the organs up to high dose group, it was not considered to be adverse.

Microscopic findings related to treatment were recorded in the liver and thymus of both sexes.

There was hepatocellular hypertrophy in both sexes of the high dose test groups (2/5M, 5/5F) and not in high dose recovery groups (0/5M, 0/5F), mainly centrilobular hypertrophy and diffusely hypertrophic cells in some locations of the female liver (1/5M, 1/5F). There were no indicators of cellular injuries such as necrosis or apoptosis nor indicator of cellular proliferation such as increased mitotic figures or polyploidy. Hence the study authors considered this finding as adaptive and not adverse.

There were increased incidence and/or severity of thymic atrophy/involution in the high dose male and female animals. As no abnormal histological findings were noted in the other lymphoid organs and tissues including spleen and lymph nodes, the study authors considered the observed effects as a secondary response to the stressful condition due to high-dose exposure of the test substance and that it was not adverse.

All treatment-related lesions disappeared after the 14-day recovery period.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established by study authors as 1,000 mg/kg bw/day in this study, based on no mortality or major signs of toxicity.

TEST FACILITY BSL Bioservice (2015a)

B.9. Genotoxicity – Bacteria

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997)
Test 1: Plate incorporation procedure/Tests 2 and 3: Pre incubation procedure

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 fraction from phenobarbital and betanaphthoflavone induced rat liver
Concentration Range in	Tests 1 and 2: 0, 78.1, 156, 313, 625, 1,250, 2,500, 5,000 µg/plate
Main Test	Test 3: 0, 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313 µg/plate
Vehicle	Dimethylsulphoxide (DMSO)
Positive Control	Sodium azide in distilled water 9-Aminoacridine in DMSO 2-Nitrofluorene in DMSO 2-Aminoanthracene in DMSO Cumene hydroperoxide in DMSO
Remarks – Method	No protocol deviations. *Escherichia coli* was not used.

RESULTS

Metabolic	*Test Substance Concentration (µg/plate) Resulting in:*			
Activation	*Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 1,580			
Test 1		> 2,500	> 2,500	Negative
Test 2		> 313	≥ 625*	Negative
Test 3		> 78.1	> 78.1	Negative
Present	> 1,580			
Test 1		> 1,250	> 2,500	Negative
Test 2		> 313	≥ 625*	Negative
Test 3		> 78.1	> 78.1	Negative

*Microcolony formation

Remarks – Results No relevant increase in the number of revertant colonies of any of the tested strains were observed following treatment with the test substance at any dose level, either with or without metabolic activation.

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

TEST FACILITY RTC (2002)

B.10. Genotoxicity – *In Vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE Analogue chemical

METHOD OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (1997)

Species/Strain	Chinese hamster
Cell Type/Cell Line	V79 cells
Metabolic Activation System	S9 mix from β-naphthoflavone/phenobarbital induced rat liver
Vehicle	MEM (minimum essential medium) cell culture medium

Remarks – Method: Minor deviations from the study plan, related to the test facility name change and use of methylmethanesulfonate (MMS) as the positive control, were not considered to have affected the outcome of the study.
Negative control: treatment medium
Positive control:
Without metabolic activation: ethyl methanesulfonate (EMS) and MMS
With metabolic activation: cyclophosphamide (CPA)

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 1.0*, 2.0*, 3.0*, 4.0, 5.0	4 hours	20 hours
Test 2	0, 0.05, 0.1*, 0.25*, 0.5*, 1.0, 2.0	21 hours	20 hours
Present			
Test 1	0, 1.0*, 2.0*, 3.0*, 4.0, 5.0	4 hours	20 hours
Test 2	0, 0.5, 1.0*, 2.5*, 3.0*, 3.5*, 4.0	4 hours	20 hours

*Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (mM) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 2.5			
Test 1		> 3.0	> 5.0	negative
Test 2		≥ 0.5	> 2.0	negative
Present	> 2.5			
Test 1		> 3.0	> 5.0	negative
Test 2		> 3.0	> 4.0	negative

Remarks – Results: There was no dose-response relationship, no biologically relevant increase in the number of structural chromosome aberrations or no statistically significant increase ($p < 0.05$) of cells with chromosomal aberrations with or without metabolic activation.

There were no statistically significant biologically relevant increase in the frequencies of polyploidy cells with or without metabolic activation.

The negative and positive controls produced satisfactory responses, confirming the activity of the S9-mix and the sensitivity of the test.

CONCLUSION: The test substance was not clastogenic to Chinese Hamster V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY: Eurofins (2015)

B.11. Genotoxicity – *In Vitro Mammalian Cell Gene Mutation Assay*

TEST SUBSTANCE: Analogue chemical

METHOD: OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test (1997)

Species/Strain: Mouse
Cell Type/Cell Line: Lymphoma/L5178Y
Metabolic Activation System: S9 mix from β-naphthoflavone/phenobarbital induced rat liver
Vehicle: Culture medium
Remarks – Method: Minor deviations from the study plan: the toxicity of the test substance was measured in pre-experiments up to a maximum concentration of 10.6 mM instead of 10 mM due to technical reason, were not considered to have affected the outcome of the study.

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Expression Time*
Absent			
Test 1	0, 0.05, 0.1, 0.2, 0.5, 0.7, 0.9, 1.1, 1.3	4 hours	48 hours
Test 2	0, 0.002, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5	24 hours	48 hours
Present			
Test 1	0, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 1.2, 1.4	4 hours	48 hours
Test 2	0, 0.15, 0.3, 0.7, 0.9, 1.1, 1.2, 1.3, 1.4	4 hours	48 hours

RESULTS

Metabolic Activation	*Test Substance Concentration (mM) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5.3	> 1.3	> 1.3	Negative
Test 2		> 0.5	> 0.5	Negative
Present				
Test 1	> 5.3	> 1.4	> 1.4	Negative
Test 2		> 1.4	> 1.4	Negative

Remarks – Results: The positive and vehicle controls gave satisfactory responses, confirming the validity of the test system.

CONCLUSION: The test substance was not clastogenic to L5178Y mouse lymphoma cells treated *in vitro* under the conditions of the test.

TEST FACILITY: BSL Bioservice (2015b)

B.12. Developmental Toxicity – Developmental Toxicity Study in Rats

TEST SUBSTANCE: Assessed chemical

METHOD: In house Non-Guideline Method. Developmental Toxicity Study in Rats

Species/Strain: Rats/Sprague-Dawley CD

Route of Administration: Oral – gavage

Exposure Information: Exposure days: once daily over days 6-19 including gestation, where day 0 was the day of detection of mating
Post-exposure observation period: none

Vehicle: Water (pH for the test substance formulation was adjusted to approximately 9.5 with sodium hydroxide)

Remarks – Method: A preliminary developmental toxicity test in Sprague-Dawley rats was performed to select dose levels for the main developmental toxicity test using test dose of 0, 125, 250, 500 and 1,000 mg/kg bw/day (6 animals per group) by gavage.

The observations at 500 and 1,000 mg/kg bw/day (weight loss and decrease in food consumption leading to the premature death of one animal at 1,000 mg/kg bw/day and severity of various clinical observations at these two dose levels such as pale liver and yellow discolouration of distended intestines were observed at one instance at 1,000 mg/kg bw/day dose) did not allow the use of either of these dose levels in the main study. However, few effects were noted for maternal toxicity at 250 mg/kg bw/day such as altered respiration appearance, piloerection and transient salivation. Therefore the proposed dose levels for the main study were established at 0, 25, 200 and 400 mg/kg bw/day.

The applicant indicated that the adverse effects seen in the preliminary test (not seen in the repeated dose oral toxicity study using the analogue chemical) might be due to sensitivity of animals and inter-lab variation.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
1	25 F	0	0/25
2	25 F	25	0/25
3	25 F	200	0/25
4	25 F	400	0/25

Mortality and Time to Death

No mortalities were observed in female animals.

Clinical observations

Clinical signs were observed in high dose females (400 mg/kg bw/day). It showed altered respiration pattern, piloerection, hunched appearance, red brown liquid and salivation from day 7 of gestation and most observations occurred during the second half of the gestation period. The condition of 4 animals of this dose level required to suspend the treatment for 1 or 2 days and 2 of these animals were killed prematurely.

At 200 mg/kg bw/day, 10 of 24 animals showed altered respiration pattern, hunched appearance and piloerection.

The clinical signs at 25 mg/kg bw/day were similar to controls.

One of the control animal was killed due to poor condition on day 7 of gestation.

At 400 mg/kg bw/day, a decrease in body weight gain was noted between days 6 and 13 of gestation, with the gains over days 6 to 9 and 9 to 13 being significantly lower. Weight gain from days 13 to 20 of gestation was statistically significantly higher. The weight gain over days 6 to 20 was lower (not statistically significant).

Group mean food consumption decreased over gestation day 10-14 at 400 mg/kg bw/day and was similar to the controls at other times. At 25 and 200 mg/kg bw/day food consumption was comparable to the controls.

Effects on Foetus

At 400 mg/kg bw/day, mean foetal weight was lower than the control mean (3.8% reduction). A slight increase in the number of foetuses with unossified 5th metacarpals and the number of sternebrae incompletely ossified was considered by the study authors related to the decrease in foetal weight.

At 25 and 200 mg/kg bw/day dose levels, there were no apparent foetal effects or mean foetal weight changes.

Remarks – Results

No obvious effects of treatment on pregnancy performance (including the incidence and survival of implants) at any dose levels were observed.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established by study authors as 200 mg/kg bw/day for foetal toxicity and 25 mg/kg bw/day for maternal toxicity in this study.

TEST FACILITY Inveresk (1998)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test
Inoculum	Activated sludge, microorganisms from a domestic waste treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Total Organic Carbon (TOC)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with good laboratory practice (GLP) standards and principles. No major deviations from the test guidelines were reported. A toxicity control was also conducted.

RESULTS

Test Substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
8	63	14	87
28	69	28	99

Remarks – Results	All validity criteria of the test guideline were satisfied. The degradation of aniline was 60% by day 8 which confirms the suitability of the activated sludge inoculum. The pH was in the range of 7.7 – 8.0 after 28 d. The percentage biodegradation of the test substance exceeded 60 % within 10 days window and hence considered to be readily degradable.
CONCLUSION	The assessed chemical is readily biodegradable under the test conditions.
TEST FACILITY	IBACON (2002)

C.2.1. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE	Assessed Chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	TOC
Remarks – Method	The test was conducted according to GLP principles. No major deviations from the test guidelines were reported. Stock solution was prepared by mixing the assessed chemical in water and filtered after stirring for 18 h. Test concentrations in a table below were prepared by diluting the filtrate. Potassium dichromate was used as a reference substance.

RESULTS

Measured Concentration (mg/L)	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0 (0)*	0 (0)*
2.68	20	0 (0)	0 (0)

5.38	20	0 (0)	1 (5)
10.7	20	1 (5)	2 (10)
21.4	20	1 (5)	4 (20)
42.8	20	6 (30)	13 (65)
85.6	20	20 (100)	20 (100)

*% immobile

EC50	31 mg/L at 48 hours (95% CL: 22 – 42 mg/L
Remarks – Results	All validity criteria were fulfilled. Dissolved oxygen was ≥ 60% of the air saturation value. The pH of test solution was in the range of 7.2 to 7.9 during 48 h. The 48 h EC50 value was calculated by probit analysis. The 24 h EC50 > 1 mg/L for daphnids exposed to potassium dichromate was within the range of expected responses.
CONCLUSION	The assessed chemical is harmful to daphnids.
TEST FACILITY	Infracor (1999)

C.2.2. Algal Growth Inhibition Test

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	Freshwater Green Alga, *Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0.10, 0.32, 1.0, 3.2, 10, 32 and 100% of WSF prepared at 100 mg/L
Auxiliary Solvent	None
Water Hardness	24mg $CaCO_3$/L
Analytical Monitoring	TOC
Remarks – Method	The test was conducted according to GLP principles. No significant deviations from the test guidelines were reported. Water Soluble Fraction (WSF) of sock solution was used for preparation of test concentrations. Potassium dichromate was used as a reference substance.

RESULTS

Biomass		*Growth*	
EbC50 (mg/L at 72 h)	*NOEbC (mg/L)*	*ErC50 (mg/L at 72 h)*	*NOErC (mg/L)*
3.1 (95%CL: 2-3.3)	1.3	13 (95% CL: 11-15)	1.3

Remarks – Results	All the validity criteria for the study were satisfied. The cell density in the control increased by a factor of 190 within 72 hours. The mean coefficient of variation for section-by-section specific growth rates in the control cultures was 9.2%. The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 3%. The Time Weighted Average (TWA) exposure concentrations were calculated to correspond to 0.42, 1.3, 4.2, 23 and 93 mg/L. Two test concentrations that were below the limit of quantification (LOQ) and 0.42 mg/L concentration were not required to determine the effect parameters. The 72 h ErC50 = 1.3 mg/L (95%CL: 1.3-1.4) was within the acceptable range for the reference substance.
CONCLUSION	The assessed chemical is harmful to algae.
TEST FACILITY	WIL (2014)

C.2.3. Toxicity to soil microorganisms – Nitrogen Transformation Test

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 216 Soil Microorganisms: Nitrogen Transformation Test
Test system	Natural soil: A field fresh silty sand soil
Exposure Period	28 d
Concentration Range	Nominal: 10, 31.6, 100, 316, 1,000 mg/L
Analytical Monitoring	Nitrate
Remarks – Method	Based on a range finding study, test concentrations were prepared from dilution of a stock solution. Cyanoguanidine was used as a reference substance.

RESULTS

Nitrate-N Content

Concentrations	*Deviation (%) compared to control*			
(mg/kg)	0 d	7 d	14 d	28 d
10	13	2	1	5
31.6	24	-6	3	15
100	15	-18	-35	3
316	19	70	3	11
1,000	12	100	100	51

-) Increase +)Inhibition;

Nitrate-N Formation Rate

Concentrations	*Deviation (%) compared to control*		
(mg/kg)	7 d	14 d	
10	-10	-6	3
31.6	-36	-10	11
100	-53	-68	-1
316	n.d	-7	9
1,000	n.d	n.d	64

-) Increase; +)Inhibition;
n.d = not determined

RESULTS	
EC50	828 mg/kg soil (95% CI; 629 – 933) mg/kg soil
Remarks – Results	All validity criteria were met. The coefficient of variation between control replicates was < 7% for nitrate-N contents during 28 days. The effect of the reference substance was ≥ 25%.as compared to the control.
CONCLUSION	The test substance is slightly toxic to soil microorganisms.
TEST FACILITY	Noack (2019a)

C.2.4. Earthworms Toxicity Study

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 222 Earthworm, Effects on Reproduction
Species	*Eisenia foetida*
	56 days
Exposure	Nominal: 3.75, 7.5, 15, 30, 60 and 120 mg/kg soil
Concentration range	None
Auxiliary solvent	The test was conducted according to GLP principles. No significant deviations from the test guidelines were reported. Following a range finding test, a definitive test was conducted. Carbendazim was used as a reference substance.
Remarks – Method	

RESULTS

Nominal Concentration (mg/kg dry weight)	*Total number of test earthworms*	*After 28 days*		*After 56 days*
		Mortality	Body weight % change	Reproduction rate (mean)
Control	80	6.25	0.07 ± 0.03	95 ± 21.1
Solvent Control	80	2.5	0.08 ± 0.01	115 ± 19.2
Pooled Control		4.35	0.07 ± 0.02	105 ± 26.6
3.75	40	17.5	0.09 ± 0.03	91± 25.2
7.5	40	2.5	0.08 ± 0.03	101 ± 10.1
15	40	7.5	0.07 ± 0.01	114 ± 35.7
30	40	7.5	0.08 ± 0.02	107 ± 6.70
60	40	7.5	0.08 ± 0.03	77 ± 13.1
120	40	7.5	0.12 ± 0.03	65 ± 15.2

56 d EC50	> 120 mg/kg dry weight soil
NOEC (reproduction)	30 mg/kg dry weight soil
Remarks – Results	All the validity criteria were met. The coefficient of variation for the control was 22%. The measured concentrations in soil were within the range of 92 to 114% of the nominal values. The significant effects of reference substance on reproduction were observed at 1 mg/kg dw soil.
CONCLUSION	The assessed chemical is slightly toxic to earthworms.
TEST FACILITY	Noack (2019b)

C.2.5. Terrestrial Plants Toxicity Study

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 208 Seedling emergence and seedling growth test
Species	Six plant species: two monocotyledon (oats, *Poaceae*; onion, *Amaryllideaceae*), and four dicotyledons (sugar beet, *Amaranthaceae*; rape, *Brassicaceae*; lettuce, *Asteraceae*; soybean, *Fabaceae*).
Exposure	21 days (28 days for onion)
Concentration range	Nominal: 62,5, 125, 250, 500 and 1,000 mg/kg dry matter (Oats, onion, lettuce and soyabean 10.24, 25.6, 64, 160, 400 and 1,000 mg/kg dry matter (Sugarbeet and rape)
Auxiliary solvent	None
Remarks – Method	The test was conducted according to GLP principles. No significant deviations from the test guidelines were reported. The test substance was incorporated into the soil in which seeds were sown.

Results

Shoot Height

Species	*NOEC (mg/kg DW)*	*EC50 (mg/kg DW)*	*CI 95% (mg/kg DW)*
Oats	500	> 1,000	-
Onion	250	> 1,000	-
Sugarbeet	1,000	> 1,000	-
Rape	400	> 1,000	-
Lettuce	125	> 250*	-
Soyabean	62.5	> 1,000	-

Shoot Fresh Weight

Species	*NOEC (mg/kg DW)*	*EC50 (mg/kg DW)*	*CI 95% (mg/kg DW)*
Oats	125	832	730 – 960
Onion	250	929	758 - >1000
Sugarbeet	500	> 1,000	-
Rape	160	956	826 - >1000
Lettuce	62.5	133	91.5 – 196
Soyabean	250	> 1,000	-

Number of Emerged seedlings

Species	*NOEC (mg/kg DW)*	*EC50 (mg/kg DW)*	*CI 95% (mg/kg DW)*
Oats	1.000	> 1,000	-
Onion	1.000	> 1,000	-
Sugarbeet	1.000	> 1,000	-
Rape	1.000	> 100	-
Lettuce	125	287	263 - 360
Soyabean	1.000	> 1,000	-

-: Not determinable; *No seedling emergence at > 250 mg/kg DW

21 d EC50 (shoot weight)	133 to > 1,000 mg/kg dry weight
Remarks – Results	The results of the control for all plant species met the required validity criteria, there was ≥ 70% seedling emergence, ≥ 90% mean survival rate of seedlings and no signs of phyto-toxicity. Lettuce was the most sensitive species. NOEC values were calculated using One Way Analysis of Variance (ANOVA) and Dunnett's Method. EC-values and graphical analysis were determined for those plant species where effects ≥ 25 % occurred.
CONCLUSION	The assessed chemical is not harmful to terrestrial plants.
TEST FACILITY	Noack (2020)

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