File No.: STD/1702

July 2021

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

2-Oxazolidinone, 3-ethenyl-5-methyl-

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:

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

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/1702	BASF Australia Ltd	2-Oxazolidinone, 3-ethenyl-5-methyl-	Yes	≤ 10 tonnes per annum	Component of printing inks, 3D printing and coatings for industrial use

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard Classification	*Hazard Statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritant (Category 2)	H315 – Causes skin irritation
Eye damage (Category 1)	H318 – Causes serious eye damage
Specific target organ toxicity – single exposure (Category 3)	H335 – May cause respiratory irritation

Human Health Risk Assessment
Under the proposed occupational settings, the assessed chemical is not considered to pose an unreasonable risk to the health of workers, provided that the recommended workplace controls are being implemented.

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 low environmental hazard and reported use pattern the assessed chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The assessed chemical should be classified as follows:
  - Acute toxicity (Category 4): H302 – Harmful if swallowed
  - Skin irritant (Category 2): H315 – Causes skin irritation
  - Eye damage (Category 1): H318 – Causes serious eye damage
  - Specific target organ toxicity – single exposure (Category 3): H335 – May cause respiratory irritation

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

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:
  - Automated processes where possible
  - Local exhaust ventilation during use, equipment cleaning and maintenance

- 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, and products and partially cured objects containing the assessed chemical:
  - Avoid contact with skin and eyes
  - Avoid inhalation of vapours, aerosols or mists

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the assessed chemical, and products and partially cured objects containing the assessed chemical:
  - Impervious gloves
  - Protective clothing
  - Eye protection
  - Respiratory protection if inhalation exposure may occur

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

- A copy of the 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.

Storage

- The handling and storage of the assessed 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 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 assessed chemical is included in products available to the public;

- the assessed chemical is intended to be used in products involving spray application;
- further information on inhalation toxicity becomes available for the assessed chemical;
- the function or use of the chemical has changed from a component of printing inks, 3D printing and coatings for industrial use;
- 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 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 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)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12, 28 Freshwater Place
SOUTHBANK VIC 3006

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

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
No details are taken to be protected information.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are not varied.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
EU (REACH)
Switzerland
New Zealand
Philippines
USA (2019)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
VMOX

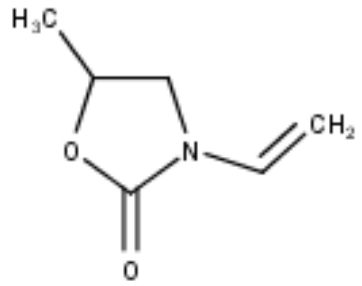
CAS NUMBER
3395-98-0

CHEMICAL NAME
2-Oxazolidinone, 3-ethenyl-5-methyl-

OTHER NAME(S)
5-Methyl-3-vinyloxazolidin-2-one

MOLECULAR FORMULA
$C_6H_9NO_2$

STRUCTURAL FORMULA



There is a chiral centre in the assessed chemical on the 5-position, indicating that the assessed chemical may have enantiomers. However, the applicant indicated that the assessed chemical originates from a racemic starting material, and preference for specific enantiomers in the final product would be unlikely.

MOLECULAR WEIGHT
127.14 g/mol

ANALYTICAL DATA
Reference NMR, GC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 94%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	2-Oxazolidinone, 3-ethenyl-4-methyl-		
CAS No.	89464-36-8	*Weight %*	< 6.0
Hazardous Properties	Expected to share the same hazard classification as the assessed chemical.		
Chemical Name	2-Oxazolidinone, 5-methyl-		
CAS No.	1072-70-4	*Weight %*	< 0.2
Hazardous Properties	Not listed on HCIS. The applicant included the following classification: H318 (Causes serious eye damage)		
Chemical Name	2-Oxazolidinone, 3-(1-ethoxyethyl)-5-methyl-		
CAS No.	123403-95-2	*Weight %*	< 0.5
Hazardous Properties	Not listed on HCIS. The applicant included the following classification: H319 (Causes serious eye irritation)		

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None identified

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless to yellow liquid

Property	***Value***	***Data Source/Justification***
Freezing Point	19 °C	Measured
Boiling Point	254 °C at 101.3 kPa	Measured
Density	1,098.3 kg/m^3 at 20 °C	Measured
Viscosity	4.28 mPa.s at 20 °C 2.52 mPa.s at 40 °C	Measured
Vapour Pressure	0.0034 kPa at 25 °C	Measured
Water Solubility	90.9 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	t½ = 1 day at 20 °C (pH 4) t½ = 0.6 day at 25 °C (pH 4) t½ = 60.2 days at 20 °C (pH 7) t½ = 37 days at 25 °C (pH 7) Stable (pH 9)	Measured
Partition Coefficient (n-octanol/water)	log Kow = 0.8 at 23 °C	Measured
Adsorption/Desorption	log K_{oc} = 1.5 at 23 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	130 °C	Measured
Flammability limits	Not determined	-

Property	*Value*	*Data Source/Justification*
Autoignition Temperature	365 °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
Thermal stability	-15.8 J/g at 117.8 °C -337.1 J/g at 255.3 °C	Measured
Self-accelerating decomposition temperature	> 75 °C	Measured

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

Reactivity
The assessed chemical is expected to react during end-use, but expected to be stable in transport and storage.

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.

The assessed chemical has a flash point of 130 ºC. Based on *Australian Standard AS1940* definitions for combustible liquid, a chemical may be considered as a Class C2 combustible liquid if the chemical has a flash point greater than 93 °C and a fire point below the boiling point.

The assessed chemical gave a heat of decomposition of > 300 J/g, and may be classified as a UN Class 4, Division 4.1 Self-reactive substance. However, a subsequent heat accumulation storage test indicated that the assessed chemical has a self-accelerated decomposition temperature of > 75 °C, and would therefore be exempt from this classification.

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 into Australia in neat form and in products containing the assessed chemical at 1–50% concentration.

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

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

PORT OF ENTRY
Melbourne, Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
BASF Australia Ltd

TRANSPORTATION AND PACKAGING
The assessed chemical will be imported in 5 kg or 220 kg steel drums. These containers will be delivered to warehouses for storage and subsequently transported to print and coating manufacturers for reformulation. The products containing the assessed chemical will then be distributed by road to customers in 20 L pails or 200 L drums. Finished products containing the assessed chemical may also be imported.

USE
The assessed chemical will be used at 1–50% concentration as a vinyl monomer in industrial printing inks, UV inkjet printing inks, 3D printing materials and coatings.

OPERATION DESCRIPTION

Reformulation
At the reformulation site, the assessed chemical in neat form will be weighed manually and added into a stainless steel blending tank, which will hold batches of 200 kg. It will be mechanically stirred with polymer resins and other components of printing or coating products. The blending tank will be enclosed during the mixing process. After the mixing is completed, the formulations containing the assessed chemical at 1–50% concentration will be pumped in a closed process into 20 L metal pails and 200 L drums for distribution to end users.

End Use
The assessed chemical at 1–50% concentration will be a component of printing and coating products for industrial use. Products containing the assessed chemical will be manually poured or pumped into the reservoirs of the application equipment. Ink products will be predominantly applied with methods such as inkjet printing and UV curing.

The 3D printing process will be carried out by applying photopolymer liquid formulations into closed 3D printing machines, with in-built filter and ventilation systems. The surface containing the resin will be light cured during the printing process and is normally 70–97% cured at this stage. Post curing of the material after cleaning will also be applied to reach full conversion.

Coating products will be predominantly applied by roller, and no spray application will be carried out. After application, the substrate will be cured by exposure to UV light. Once inks or coatings are added to the application equipment, the processes are expected to be fully automated. Residues of inks and coatings in the container will be washed and collected or sent to licenced drum recyclers.

The assessed chemical will be applied on substrates including metal, wood and paper. The applicant estimated that for inks and coatings, 5% of the imported quantity will be used on metal, 60% will be used on plastics, and 35% will be used on paper. The 3D printed material would mostly be used for prototyping, automotive, engineering plastics, aerospace and transportation material.

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 workers	1–5	10–20
Reformulation workers	8	20–40
Cleaners	0.5–1	10–20
Quality control	1–2	10–20
End users	2–3	200–240

EXPOSURE DETAILS

Transport and Storage
Transport and storage workers may come into contact with the assessed chemical in neat form (as imported) or at 1–50% concentration (in end use formulations/products), only in the unlikely event of accidental breaching of containers.

Reformulation
At reformulation sites, dermal and ocular exposure to the assessed chemical in neat form may occur when weighing and transferring the assessed chemical in liquid form to the blending tank or during equipment cleaning and maintenance. Inhalation exposure is not expected unless aerosols are generated during reformulation. According to the applicant, exposure to the assessed chemical during reformulation will be minimised through the use of good general ventilation and personal protective equipment (PPE). This may include gloves, safety goggles, coveralls, and respiratory protection if ventilation is inadequate.

End use
At end use sites there may be dermal or ocular exposure to inks and coatings containing the assessed chemical at 1–50% concentration during transfer, application and equipment cleaning processes. Application of the products will occur at industrial sites, and is expected to use highly automated processes. Significant inhalation exposure is not expected unless aerosols are generated during the processes. According to the applicant, the potential for exposure during manual processes such as transfer and cleaning is expected to be minimised through the use of PPE. This includes coveralls, gloves and goggles, as well as appropriate respiratory protection where ventilation is inadequate.

The 3D printing application of products containing the assessed chemical will be carried out within closed machines, with built-in filter and ventilation systems. The assessed chemical is expected to be light-cured during the printing process, and will be additionally cured after processing and cleaning. Therefore there could be incidental dermal or ocular exposure of workers to the chemical during finishing of the final objects, as curing is not complete at this stage.

Once dried and cured, the assessed chemical will be reacted into the matrix. Residual traces of the assessed chemical that are not reacted will become part of the solid matrix of the ink, coating or 3D object and are not expected to be available for exposure.

6.1.2. Public Exposure
The inks, 3D printed material, and coatings containing the assessed chemical at 1–50% concentration will be used in industrial settings only and will not be made available to the public. Once the products have been dried and cured, the assessed chemical will be bound into an inert solid matrix and is not expected to be available for exposure.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the assessed chemical are summarised in the following table. For details of the studies, refer to Appendix B.

Endpoint	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LD50 > 300 and < 2,000 mg/kg bw; harmful
Acute dermal toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity
Skin corrosion/irritation – *in vitro* – combined study using Epiderm model	Irritating
Eye irritation – *in vitro* – combined study using BCOP and EpiOcular tests	Corrosive or severely irritating
Skin sensitisation – mouse local lymph node assay	No evidence of sensitisation up to 2% concentration
Combined repeated dose oral toxicity with reproductive/developmental toxicity – 28-day, rat	NOAEL (systemic, 28 days) = 50 mg/kg bw/day NOAEL (reproduction/developmental) = 150 mg/kg bw/day
Repeated dose oral toxicity – 90-day, rat	NOAEL (systemic, 90 days) = 15 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	Non mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test	Non mutagenic
Genotoxicity – *in vitro* mammalian cell micronucleus test	Non genotoxic
Genotoxicity – *in vitro* mammalian cell gene mutation test using the Thymidine Kinase Gene	Non mutagenic
Prenatal developmental toxicity – rat	NOAEL (maternal) = 15 mg/kg bw/day NOAEL (reproductive) = 150 mg/kg bw/day NOAEL (developmental) = 15 mg/kg bw/day

Toxicokinetics, Metabolism and Distribution
No toxicokinetic data were submitted for the assessed chemical.

Based on its molecular weight (< 500 g/mol) and partition coefficient (log Kow = 0.8), the assessed chemical is expected to be absorbed via all routes of exposure.

Acute Toxicity
The assessed chemical was harmful via the oral route (LD50 between 300 and 2,000 mg/kg bw in rats). The assessed chemical was found to be of low acute toxicity to rats via the dermal route.

No acute inhalation toxicity data were provided for the assessed chemical. In a 14-day inhalation study in rats, significant respiratory irritation was seen in the form of histopathological changes in the nasal cavity (see Repeated Dose Toxicity section below). The assessed chemical is also classified for severe eye irritation (see Irritation and Sensitisation section below). The applicant stated that irritation to the respiratory tract is likely to occur after a single exposure, as would normally occur with other irritating substances. Based on the effects in the 14-day inhalation study, the relatively low concentration (0.096 mg/L) at which these effects occurred, and the known irritating effects of the assessed chemical, a classification of Specific target organ toxicity – single exposure (Category 3) is considered warranted.

The assessed chemical has a sufficiently low kinematic viscosity to meet one of the classification requirements for potential aspiration hazards. However, its water solubility is moderate and it is not of comparable chemical structure to any chemical classes associated with aspiration hazards that are discussed in the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*. Available acute and repeated dose toxicity studies did not indicate any macroscopic nor microscopic findings on pneumonia or pulmonary injury. Therefore, the assessed chemical is not considered likely to cause human aspiration toxicity hazard.

Irritation and Sensitisation
In a combined skin corrosion/irritation study using the EpiDerm model, the assessed chemical was irritating to the skin under the conditions of the test.

According to the results of a combined eye irritation *in vitro* assay using BCOP and the EpiOcular tests, the assessed chemical was considered to be either corrosive (equivalent to causing severe eye damage) or irritating to eyes. Overall, the Category 1 classification is considered to be warranted for the assessed chemical.

The assessed chemical was not a skin sensitiser in a local lymph node assay (LLNA) when tested up to 2% concentration.

Repeated Dose Toxicity
In a GLP compliant 90-day study with a 28-day recovery period, Wistar rats (10/sex) were administered the assessed chemical by gavage at 0, 15, 50, 175 mg/kg bw/day, 7 days/week. Reductions in mean body weight (< 10% reduction compared to controls groups) during treatment at high dose and during the recovery period were considered adverse effects. Liver and nasal cavity were target organs for pathology evidenced by reports of increased liver weights and histopathological changes of the liver and nasal cavity at the high and mid dose, respectively. During the recovery period, the liver effects were reversed. Therefore, a systemic no observed adverse effect level (NOAEL, 90 days) for this study was set at 15 mg/kg bw/day, based on adverse histopathological effects on the nasal cavity of both sexes of the rats at ≥ 50 mg/kg bw/day. These effects included multifocal atrophy in respiratory epithelium, concretions, and degeneration/regeneration, with no significant reversibility during recovery.

In a combined repeated dose toxicity study with reproductive/developmental toxicity screening study, Wistar rats (10/sex) were treated by gavage with the assessed chemical at 0, 15, 50, 150 mg/kg bw/day, in males for 29 days and in females for 51 days. A NOAEL (28 days) for systemic toxicity was established as 50 mg/kg bw/day, based on the decreased body weight in male animals and increased blood cell count in female animals at 150 mg/kg bw/day.

In a short-term (14 days) repeated dose whole body inhalation screening study in rats, exposure to a saturated vapour concentration (0.096 mg/L/6h/day, 5 days/week) showed no mortality, Histological changes in the nasal cavity were significant, consisting of degeneration/regeneration of the olfactory epithelia and loss of mucous cells.

Based on available data, the assessed chemical may cause adverse effects to the nasal cavity upon repeated exposure. However, it is not known whether these effects, seen in a 90-day oral gavage study, are due to local or systemic toxicity. The adverse effects observed in the nasal cavity in the repeated dose oral study could be due to repeated contact with the gavage tube containing an irritating test substance. Upon removal of the gavage tube, its contents can be aspirated or liberated by respiratory airflow, and parts of the test substance can be delivered into the oesophagus, oropharynx or nasal cavity (Damsch et al., 2011). Observed effects in the respiratory tract would be consistent with the known irritating effects of the assessed chemical. However the potential of the assessed

chemical to cause systemic toxicity (effects on the respiratory tissues occurring after gastrointestinal absorption), cannot be completely ruled out.

Reproductive/developmental toxicity
In the combined repeated dose toxicity study with reproductive/developmental toxicity screening (see above), the fertility, pup delivery and pup growth were not affected by treatment. Stages of spermatogenesis of high dose males were comparable to those of the controls. The NOAEL for reproductive/developmental effects was set at 150 mg/kg bw/day, the highest dose level tested.

In a prenatal developmental toxicity study, female rats were exposed by gavage to the assessed chemical at 15, 50 and 150 mg/kg bw/day during gestation days (GD) 6–19. There was evidence of systemic maternal toxicity, such as reductions in water and food consumption, in body weight gain and pathological changes of liver metabolism at ≥ 50 mg/kg bw/day. The maternal NOAEL was established as 15 mg/kg bw/day in this study, and the study authors concluded that the developmental NOAEL was 150 mg/kg bw/day, the highest dose tested. There is some uncertainty regarding the NOAEL for developmental effects. The mean foetal weights of both sexes were statistically significantly reduced at ≥ 50 mg/kg bw/day, however these decreases were seen in the presence of maternal toxicity, and were not accompanied by an equivalent reduction of gravid uterine weight. Therefore, a conservative developmental NOAEL was established as 15 mg/kg bw/day.

Mutagenicity/Genotoxicity
The assessed chemical was not mutagenic in a bacterial reverse mutation test or in two *in vitro* mammalian cell gene mutation tests conducted using the HRPT locus and Thymidine Kinase Gene. The assessed chemical was not genotoxic in an *in vitro* mammalian cell micronucleus test.

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

Hazard Classification	***Hazard Statement***
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritant (Category 2)	H315 – Causes skin irritation
Eye damage (Category 1)	H318 – Causes serious eye damage
Specific target organ toxicity – single exposure (Category 3)	H335 – May cause respiratory irritation

6.3. Human Health Risk Characterisation
The assessed chemical is harmful via the oral route. It causes serious damage to the eyes and is irritating to the skin. It is also expected to cause respiratory irritation after single inhalation exposure, and adverse effects on the nasal cavity after repeated (14 day) inhalation.

6.3.1. Occupational Health and Safety

Reformulation
During reformulation, workers may come into contact with the assessed chemical in neat form during transfer, maintenance, and cleaning operations. The mixing and blending process during reformulation is expected to be automated and enclosed. Control measures indicated on the SDS for the assessed chemical include use of adequate general ventilation and suitable PPE such as coveralls, safety boots, protective gloves and safety glasses, to minimise worker exposure.

End-use
During end-use, professional workers may come into contact with the assessed chemical at 1–50% concentration during transfer, application and cleaning processes. Some of the printing and coating application processes are automated and thus minimal exposure would be expected. Exposure and risk would be further mitigated by use of control measures such as local ventilation and PPE, as indicated on the SDS provided. Some workers may be exposed to 3D printed objects prior to full curing of the objects, and in this case, controls such as PPE would be needed until full curing had occurred, in order to reduce the exposure of those workers.

Overall, based on the proposed occupational settings and recommended workplace controls, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

6.3.2. Public Health

Products containing the assessed chemical will not be available to the public. Members of the public may come into contact with articles treated with finished products containing the assessed chemical. However, the assessed chemical in cured form is expected to be bound within the inert matrix and will not be available for exposure.

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

During reformulation the residues of the assessed chemical in import containers and processing equipment are rinsed with suitable solvent, collected and recycled into the next batch of product. Release from the reformulation process is limited to accidental spills which are to be collected and disposed of via landfill.

RELEASE OF CHEMICAL FROM USE

The assessed chemical is to be used in an industrial setting. The assessed chemical will be applied to metal, plastic or paper substrates or used for 3D printing.

The assessed chemical used within ink products will be bound within the cured ink matrix upon use. Any spills are expected to be adsorbed onto a suitable material and collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM DISPOSAL

Most of the assessed chemical is expected to share the fate of the articles to which it has been applied or incorporated within. These will either be recycled or disposed of to landfill at the end of their useful life.

For ink products printed on paper substrates the assessed chemical could be released to the aquatic environment from paper recycling processes. The applicant has estimated that printing on paper accounts for 35% of the import volume of the assessed chemical. A recent Australian waste report found the average paper recycling rate of 60% (Blue Environment Ltd., 2016). Therefore, in the worst case scenario, up to 21% of the import volume of the assessed chemical could be released to the aquatic environment from paper recycling processes.

Approximately 0.2% of the import volume is expected to remain in the packaging material which will be disposed of via landfill.

7.1.2. Environmental Fate

In landfill, the assessed chemical will be present as cured solids and will be neither bioavailable nor mobile.

During the metal recycling process, the assessed chemical is expected to be thermally decomposed to form water and oxides of carbon and nitrogen.

During paper recycling processes, waste paper is repulped using a variety of chemical treatments which, amongst other things, enhance ink detachment from the fibres. Waste water from paper recycling processes containing the assessed chemical is expected to be treated at an onsite wastewater treatment plant before potential release to sewers or surface waters. Paper recycling occurs at facilities located throughout Australia and it is anticipated that such releases will occur over working days.

Due to its high measured water solubility (90.9 g/L) and the estimated low log Kow (0.8), the assessed chemical is not expected to absorbed to sludge significantly at STPs (Struijs, 1996). For details of the water solubility study conducted on the assessed chemical, refer to Appendix A. The assessed chemical is not expected to bioaccumulate based on its low log Kow. In landfill and water, the assessed chemical is expected to eventually degrade via biotic and abiotic processes to form water and oxides of carbon and nitrogen.

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 21% 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/Manufactured Volume	10,000	kg/year
Proportion expected to be released to sewer	21%	
Annual quantity of chemical released to sewer	2100	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	8.08	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:	1.66	µg/L
PEC - Ocean:	0.17	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 assessed 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 1.66 µg/L may potentially result in a soil concentration of approximately 0.011 mg/kg. Assuming accumulation of the assessed chemical in soil for 5 and 10 years under repeated irrigation, the concentration of assessed chemical in the applied soil in 5 and 10 years may be approximately 0.0552 mg/kg and 0.110 mg/kg, respectively.

The actual concentration is likely to be lower as the assessed chemical will be present as cured solids and not significantly available for release during paper recycling.

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	LC50 > 120 mg/L	Not harmful to fish
Daphnia Toxicity	EC50 > 120 mg/L	Not harmful to aquatic invertebrates
Algal Toxicity	EC50 > 120 mg/L	Not harmful to algal growth
Inhibition of Bacterial Respiration	IC50 = 110 mg/L	Not inhibitory to bacterial respiration

Based on the above ecotoxicological endpoints for the assessed chemical, it is not expected to be harmful to aquatic organisms. Therefore, the assessed chemical is not formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* for acute and chronic toxicities (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration was not calculated as the assessed chemical is not harmful to aquatic organisms.

7.3. Environmental Risk Assessment

A Risk Quotient was not quantified as the assessed chemical is not harmful to aquatic organisms. Although there will be some release of the assessed chemical to the aquatic environment this is unlikely to be eco-toxicologically significant. After curing, the assessed chemical it will be irreversibly incorporated into an inert matrix which is not expected to be mobile, bioavailable or bioaccumulative. On the basis of the low aquatic toxicity and proposed use pattern, the assessed chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point 19 °C

Method OECD TG 102 Melting Point/Melting Range
Remarks Differential scanning calorimetry (DSC) was used.
Test Facility BASF (2015a)

Boiling Point 254 °C at 101.3 kPa

Method OECD TG 103 Boiling Point
Remarks Dynamic method was used.
Test Facility BASF (2015a)

Density 1,098.3 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids
Remarks An oscillating density meter was used.
Test Facility BASF (2015a)

Viscosity 4.28 mPa.S at 20 °C
2.52 mPa.S at 40 °C

Method OECD TG 114 Viscosity of Liquids
Remarks A capillary viscometer was used.
Test Facility BASF (2015a)

Vapour Pressure 0.0034 kPa at 25 °C

Method OECD TG 104 Vapour Pressure
EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks Gas saturation method was used.
Test Facility BASF (2015a)

Water Solubility 90.9 g/L at 20 °C

Method OECD TG 105 Water Solubility
EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks Flask Method
Test Facility BASF (2015b)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.
EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH

pH	*T (°C)*	*$t_{½}$ (days)*
4	20	1
4	25	0.6
7	20	60.2
7	25	37

Remarks HPLC system with UV/VIS detector. Due to stability of the test solution at 50°C for pH 9, no further experiments were performed.

Test Facility BASF (2015c)

Partition Coefficient (n-octanol/water) log Kow = 0.8 at 23 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method.
Test Facility	BASF (2015d)

Adsorption/Desorption log K_{oc} = 1.5 at 23 °C

Method	OECD TG 121 Adsorption Coefficient using HPLC
Remarks	
Test Facility	BASF (2015e)

Flash Point 130 °C at 100.8 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	A Pensky-Marten closed cup apparatus procedure was used.
Test Facility	Chilworth (2015)

Autoignition Temperature 365 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	An AIT (Autoignition) System was used. There was a lag time of 3 seconds before ignition.
Test Facility	Chilworth (2015)

Stability Testing -15.8 J/g at 117.8 °C, -337.1 J/g at 255.3 °C

Method	Screening Test for Thermal Stability
Remarks	Differential scanning calorimetry (DSC) was used. As the test substance did not give a heat of decomposition > 500 J/g, it was not classified for a UN Class 1 Explosive substance, but as its heat of decomposition was > 300 J/g, it may be classified as a UN Class 4, Division 4.1 Self-reactive substance.
Test Facility	Chilworth (2015)

Self-accelerating decomposition temperature > 75 °C

Method	UN Test H.4. Heat accumulation storage test
Remarks	A Dewar with a thermocouple was used. The test substance did not reach a temperature of more than 6 higher than the oven temperature. Therefore, its SADT was given as being greater than the highest storage temperature. The test substance is therefore exempt from classification as a UN Class 4, Division 4.1 Self-reactive substance.
Test Facility	Chilworth (2015)

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 (2001) EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Wistar Crl:WI (Han)
Vehicle	Corn oil
Remarks – Method	GLP Certificate. No significant protocol deviation.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 F	2,000	3/3
2	3 F	300	0/3
3	3 F	300	0/3

LD50	> 300 and < 2,000 mg/kg bw
Signs of Toxicity	Two animals treated with 2,000 mg/kg bw died after application of the assessed chemical, and the remaining one was euthanized within 5 hours of treatment. Signs of toxicity before death included poor general state, dyspnea, apathy, abdominal position and atonia. All animals in both 300 mg/kg bw dose groups survived. All animals showed an impaired general state and piloerection. Dyspnea, abdominal position and cowering was observed in some animals on the first day after dosing.
Effects in Organs	Yellow discolouration of stomach contents, red discolouration of the glandular stomach and small intestines were observed in all deceased animals from the 2,000 mg/kg dose group during necropsy. No abnormalities in histopathology were noted in any surviving animals.
Remarks – Results	All surviving animals showed expected gains in body weight over the study period.

CONCLUSION	The assessed chemical is harmful via the oral route.
TEST FACILITY	Bioassay (2014a)

B.2. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 402 Acute Dermal Toxicity– Limit Test (1987) EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/Wistar Crl:WI (Han)
Vehicle	None. The assessed chemical was applied undiluted.
Type of dressing	Semi-occlusive
Remarks – Method	GLP Certificate. No significant protocol deviation.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity – Local	No local effects were noted.
Signs of Toxicity – Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks – Results	All male animals showed expected body weight gain over the observation period. Three female animals lost weight and one did not gain weight in the first week, but reached the expected body weight range in the second week.
CONCLUSION	The assessed chemical is of low acute toxicity via the dermal route.
TEST FACILITY	Bioassay (2014b)

B.3. Skin Corrosion and Irritation – *in vitro*

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 431 *In vitro* Skin Corrosion: Human Skin Model Test (2013) OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2013)
Vehicle	None. The assessed chemical was applied undiluted.
Remarks – Method	GLP Certificate No significant protocol deviation. EpiDerm Model. Negative control (de-ionised water) and positive control (potassium hydroxide, 8 mol/L for corrosion test; 5% sodium dodecyl sulfate solution for irritation test) were run concurrently with the assessed chemical.

RESULTS

Corrosion test - 3 Minute Exposure

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	2.047	100	8.34
Test substance	1.770	86	2.12
Positive control	0.438	21	0.21

Corrosion test - 1 Hour Exposure

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	1.780	100	1.41
Test substance	0.536	30	13.15
Positive control	0.127	7	0.21

Irritation test

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	2.547	100	6.51
Test substance	0.534	21	11.00
Positive control	0.068	3	0.29

OD = optical density; SD = standard deviation

Remarks – Results	In the skin corrosion test, the relative mean tissue viability was ≥ 50% after the 3 minute treatment with the assessed chemical and ≥ 15% after the 1 hour treatment. Based on these results, the test substance is categorised as non-corrosive. In the skin irritation test, the relative mean tissue viability was ≤ 50% after treatment with the assessed chemical. Based on these results, the test substance is categorised as irritating.

In case direct MTT reduction occurred, freeze-dried control tissues were included for the test substance and the positive and negative controls. However, these tissues did not indicate an increased MTT reduction and were not used for the viability calculation.

The negative control and positive controls gave values within the historical control values, and the tissue variability met the acceptance criteria. Therefore, it is concluded by the study authors that the test conditions of this study were adequate and functioned properly.

CONCLUSION: The assessed chemical was considered irritating to the skin under the conditions of the combined tests.

TEST FACILITY: BASF (2014a)

B.4. Eye Irritation – *in vitro*

TEST SUBSTANCE: Assessed chemical

METHODS: 1) OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
2) Determination of Ocular Irritation Potential Using the EpiOcular™ Model (similar to the later OECD TG 492)

Vehicle: None. The assessed chemical was applied undiluted.

Remarks – Method: GLP Certificate
No significant protocol deviation.
Negative control (de-ionised water) and positive control (dimethylformamide for BCOP test; methyl acetate for EpiOcular test) were run concurrently with the assessed chemical.

RESULTS

BCOP Test

Test Material	*Mean Opacities of Triplicate Tissues (SD)*	*Mean Permeabilities of Triplicate Tissues (SD)*	*IVIS (SD)*
Vehicle control	1.6 (0.8)	0.002 (0.002)	1.6 (0.8)
*Test substance**	53.7 (2.4)	0.254 (0.097)	57.5 (1.5)
*Positive control**	102.7 (0.5)	1.218 (0.386)	121.0 (5.5)

SD = Standard deviation; IVIS = in vitro irritancy score
* Corrected for background values

EpiOcular Test

Test material	*Mean OD_{570} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.935	100
Test substance	0.137	7
Positive control	0.421	22

OD = optical density

Remarks – Results: Because the IVIS was > 55 after the treatment with the assessed chemical in the BCOP test, it is categorised as an ocular corrosive or severe irritant, according to the test guideline. Although the mean IVIS value of 57.5 is close to the cut-off value of 55, the results were not considered borderline as all IVIS values (57.9, 58.7 and 55.7) are concordant and above the cut-off level of 55.

Because the relative mean tissue viability was ≤ 60% after treatment with the assessed chemical in the EpiOcular test, it is categorised as irritating according to the test criteria.

For the BCOP test, a histopathological examination of the corneas was carried out and indicated severe effects.

For the Epiocular test, freeze-dried control tissues were included for the test substance and the positive and negative controls in case direct MTT reduction occurred. However these tissues did not indicate an increased MTT reduction and were not used for the viability calculation.

The results from the negative control and positive control in both studies were within the historical control values and all acceptance criteria were met. Therefore, the test conditions of this study were considered adequate and functioned properly.

CONCLUSION The assessed chemical was an ocular corrosive or severely irritating to the eyes under the conditions of the combined test.

TEST FACILITY BASF (2014b)

B.5. Skin Sensitisation – LLNA

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010)
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	Propylene glycol
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexyl cinnamaldehyde.
Remarks – Method	A series of pre-tests at 100%, 50%, 25%, 10%, 5% and 2% concentration was carried out to determine concentrations for the main test. Animals treated with 5% or higher concentration showed erythema on the ears and signs of systemic toxicity. GLP Certificate. No significant protocol deviation.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*Proliferative Response (DPM/lymph node)*	*Stimulation Index (SI) (test/control ratio)*
Test Substance			
0 (vehicle control)	5 F	236.4	1.00
0.5	5 F	493.1	2.09
1	5 F	653.9	2.77
2	5 F	566.4	2.40
Positive Control			
0 (vehicle control)	not reported	776.9	1.00
5	not reported	1500.4	1.93
10	not reported	2058.9	2.65
25	not reported	7367.3	9.48

EC3	Not determined
Remarks – Results	No deaths or signs of systemic toxicity were observed in the main study. On day 2, the animals from the 2% dose group showed an erythema score of 1 on the ear skin. A statistically significant increase in DPM value and lymph node cell count was observed in all treated groups, However, this was not

	considered to be biologically relevant by the study authors as the SI calculated did not exceed the threshold value of 3.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the assessed chemical at up to 2% concentration.
TEST FACILITY	Harlan (2015)

B.6. Combined Repeat Dose Oral Toxicity with Reproductive/Developmental Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (1996) US EPA OPPTS Guideline 870.3650 Combined Repeat Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (2000)
Species/Strain	Rat/Wistar Crl:WI (Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: Males: 29 days (2-week premating, during mating, and approximately 1-week post-mating until one day before sacrifice) Females: 51 days (2-week pre-mating, during mating, gestation days (GD) 0–20, post-natal days (PND) 0–4 or lactation days (LD) 0–15 until one day before sacrifice) Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Corn oil
Remarks – Method	GLP Compliant statement. No protocol deviations. Doses were chosen by the sponsor.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 F, 10 M	0	1/20
Low Dose	10 F, 10 M	15	0/20
Mid Dose	10 F, 10 M	50	0/20
High Dose	10 F, 10 M	150	0/20

Mortality and Time to Death

There were no unscheduled deaths of animals in all dose groups, except for one female in the control group that died during anaesthesia for blood sampling.

Clinical Observations

Slight to severe salivation after treatment was seen in males and females, mostly in the mid and high dose groups. The study authors considered this to be caused by the taste or irritant properties of the test substance. No test substance related changes were seen in the functional observation battery (case vs open field observations and sensory tests) or motor activity measurements.

Male rats at 150 mg/kg bw/day showed decreased food consumption (15.5%) and body weight gain (48.7%) during pre-mating, and decreased body weight during entire the study period (5.7%) and at termination (6%), compared with controls.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Female rats at 150 mg/kg bw/day showed increases in total white blood cell, absolute neutrophil and lymphocyte counts, compared with the controls. Although the increases were not statistically significant, they were considered by the study authors to be treatment-related. Some blood parameters were statistically significantly increased in high dose males, but were within the historical controls.

No treatment-related changes were observed in clinical chemistry or urinalysis parameters.

Effects in Organs
In the histopathological examination, 7/10 females in the high dose group showed a minimal centrilobular hepatocellular hypertrophy and 1/10 periportal vacuolation. This was regarded as treatment-related but not adverse by the study authors.

All other findings were biologically equally distributed over the control and treatment groups, and were considered to be incidental or spontaneous in nature. There were no significant differences in the mean absolute or relative organ weights between test animals and the controls. Stages of spermatogenesis in the testes of high dose males were comparable to those of the controls.

Reproductive toxicity
The fertility index of both genders ranged between 90–100%, with no significant dose-dependent change compared to the control. The gestation index and rate of live birth indices were 100% in all treated animals. The post-implantation loss was 0.9% in the control group, and was 10.9%, 2.4% and 6.0% in the low, mid and high dose groups respectively. These percentages were within the range of historical control data.

Effects on 1st Filial Generation (F1)
The mean number of delivered F1 pups per dam were similar for all groups, and within the historical control range. Pup viability was 100% in the control and mid dose groups, 98.4% in the low dose group and 99.2% in the high dose group. The sex ratio of the low and high dose group were slightly offset (40.4:59.6 and 40.9:59.1 for males to females, compared to 55.1:44.9 for controls), but this change was not statistically significant and was regarded as spontaneous in nature by the study authors.

No statistically significant changes were seen in pup weight at day 1 or day 4 between the test groups and the controls. Pup mean body weight change between day 1 and day 4 was significantly decreased in pups from the mid dose group only, compared to the control group. However non-statistically significant reductions in pup weight changes were also observed in the low and high dose groups. These effects are reported as likely caused by a high mean pup body weight change in the control group, compared to the historical controls.

Three male and one female runt were seen in the low dose group, one male runt was seen in the mid dose group, and one male and three female runts were seen in the high dose group. These values were considered by the study authors to be within the range of the normal biological variation.

One male pup and one female pup from the low dose group were found dead or cannibalised, and one female pup from the high dose group was found dead, prior to the scheduled sacrifice. No test substance related effects were seen at pup necropsy.

Remarks – Results
There were signs of adverse systemic effects in rats at 150 mg/kg bw/day. No fertility, reproductive performance or developmental effects were identified.

CONCLUSION
The no-observed-adverse-effect level (NOAEL) for systemic toxicity was established as 50 mg/kg bw/day, based on the decreased body weight in male animals and increased blood cell count in female animals at 150 mg/kg bw/day. The NOAEL for reproductive and developmental toxicity was established as 150 mg/kg bw/day under the conditions of this study.

TEST FACILITY BASF (2016a)

B.7. Repeat Dose Oral Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents (2018) US EPA OPPTS Guideline 870.3100 90-Day Oral Toxicity in Rodents (1998)

Species/Strain	Rat/Wistar 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: 28 days
Vehicle	Corn oil
Remarks – Method	GLP compliant. No protocol deviations. Doses were chosen by the sponsor.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 F, 10 M	0	1/20
Low Dose	10 F, 10 M	15	0/20
Mid Dose	10 F, 10 M	50	0/20
High Dose	10 F, 10 M	175	0/20
Control Recovery	10 F, 10 M	0	0/20
High Dose Recovery	10 F, 10 M	175	0/20

Mortality and Time to Death

There were no deaths in the treated animals. One control male rat was found dead (with red discoloration of lungs and red effusion), probably due to a gavage error.

Clinical Observations

Within 2 hours after treatment, slight to moderate salivation was seen in mid- (12/20 animals) and high-dose (38/40) animals, which were considered related to the taste or irritant properties of the test substance.

The mean body weight was reduced in high-dose rats during treatment and even more during the recovery period (reduction of 5.8% on Day 91 and up to 6.7% between Days 98–119 in males, and reduction up to 4.6% between Days 42–84 and 5.7% on Day 112 in females, respectively).

Reductions in body weight gain were seen from Day 77 in males (7.7%) and from Day 42 in females (6.7%).

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

A range of pathological changes were reported at 175 mg/kg bw/day, including increased levels of HDL-cholesterol and calcium oxalate and triple phosphate crystals in the urine in both sexes of rats, increased levels of absolute neutrophils and monocytes, inorganic phosphate and ketone bodies in male rats, and increased levels of cholesterol and triglycerides and platelets in female rats.

Effects in Organs

At the high dose, increased mean relative liver weights (up to 12.7% increase compared to the control group) were observed in both sexes of rats and increased absolute liver weights (9.1% increase compared to the control group) were also reported in female rats. In the recovery group, mean liver weights of high dose males were comparable to the controls, and the mean liver weights of females showed some signs of recovery (5.0% increase compared to the control group), Histopathological changes in the treatment group included centrilobular hepatocellular hypertrophy (9/10 male rats) and accompanied fatty change (4/10 male rats). These histopathological effects in the liver were no longer observed in the high dose recovery group. However, single cell necrosis was observed in 1/10 high dose recovery females.

Pronounced histopathological findings were seen at all levels of the nasal cavity (e.g. multifocal atrophy in respiratory epithelium, concretions, and degeneration/regeneration) in both sexes of rats at ≥ 50 mg/kg bw/day, with various degrees of severity reported during treatment and recovery. The study authors noted that structures of the olfactory epithelium, the goblet cells, and Bowman's glands were most affected.

Remarks – Results

The target organs for toxicity were the liver and nasal cavity. The liver effects had shown some reversibility during the recovery period.

CONCLUSION
The systemic NOAEL was established as 15 mg/kg bw/day in this study, based on the adverse histopathological effects on the nasal cavity of both sexes of the rats at ≥ 50 mg/kg bw/day (including multifocal atrophy in respiratory epithelium, concretions, and degeneration/regeneration).

TEST FACILITY BASF (2020a)

B.8. Genotoxicity – Bacteria

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997)
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria
Plate incorporation procedure (test 1 and test 2 in the absence of metabolic activation)
Pre incubation procedure (test 2, in the presence of metabolic activation)

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9-mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) Test 1: 5 – 5,000 µg/plate b) Test 2: 5 – 5,000 µg/plate
Vehicle	Water
Remarks – Method	GLP Certificate. Doses were assumed to be at 100% purity. Vehicle control and positive controls were run concurrently with the test substance.

RESULTS

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

Remarks – Results No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, at any test concentration, either with or without metabolic activation.

The positive and vehicle controls gave satisfactory responses confirming the validity of the test system.

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

TEST FACILITY Covance (2014)

B.9. Genotoxicity – *in vitro* mammalian cell gene mutation test

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test (1997)
HPRT Locus Assay

Species/Strain	Chinese Hamster
Cell Type/Cell Line	CHO (Chinese hamster ovary) cell line
Metabolic Activation System	S9-mix from phenobarbital/β-naphthoflavone induced rat liver

Vehicle	Culture medium
Remarks - Method	GLP certificate.

A dose range-finding study was carried out at 5.1 – 1,300 µg/mL. No cytotoxicity or precipitation was observed in the presence and absence of the S9 mix. The dose selection for the main experiments was based on concentrations in the range-finding study.

Test 2 for this study was discontinued due to contamination. A repeat study designated as Test 3 was performed.

Vehicle control and two positive controls (ethyl methanesulfonate without metabolic activation and 7,12-dimethylbenz[a]anthracene with metabolic activation) were run concurrently with the assessed chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0*, 81.3, 162.5*, 325*, 650*, 1300*	4 h	7 – 9 days	6 – 7 days
Test 3	0*, 40.6, 81.3, 162.5*, 325*, 650*, 1300*	4 h	7 – 9 days	6 – 7 days
Present				
Test 1	0*, 250*, 500*, 1000*, 1300*	4 h	7 – 9 days	6 – 7 days
Test 3	0*, 250*, 500*, 1000*, 1300*	4 h	7 – 9 days	6 – 7 days

* Selected for mutation frequency (MF) 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	> 1,300	> 1,300	> 1,300	Negative
Test 3	-	> 1,300	> 1,300	Negative
Present				
Test 1	> 1,300	> 1,300	> 1,300	Negative
Test 3	-	> 1,300	> 1,300	Negative

Remarks - Results	The assessed chemical did not lead to a statistically significant increase in the number of mutation frequencies at the HPRT locus, either in the presence or absence of metabolic activation. The acceptance criteria set by the study authors regarding concentration levels and the parameters for positive and negative controls were all met. The increase in the frequencies of mutant colonies induced by the positive control demonstrated the sensitivity of the test method and the metabolic activity of the S9 mix.
CONCLUSION	The assessed chemical was not mutagenic to Chinese Hamster ovary cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BASF (2015f)

B.10. Genotoxicity – *in vitro* mammalian cell micronucleus test

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 487 *In vitro* Mammalian Cell Micronucleus Test (2014)
Species/Strain	Chinese Hamster
Cell Type/Cell Line	V79 cell line

Metabolic Activation System	S9-mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Culture medium
Remarks - Method	GLP Certificate The dose selection for the main experiments was based on a preliminary range finding study of a mammalian cell gene mutation study conducted by BASF (see above). Vehicle and positive controls (ethyl methanesulfonate (EMS) without metabolic activation and cyclophosphamide with metabolic activation) were run concurrently with the assessed chemical.

Metabolic Activation	*Test Substance Concentration (µL/mL)*	*Exposure Period*	*Expression Time*
Absent			
Test 1	0*, 40.6, 81.3, 162.5, 325*, 650*, 1300*	4 hours	24 hours
Test 2	0*, 162.5, 325*, 650*, 1300*	24 hours	24 hours
Present			
Test 1	0*, 40.6, 81.3, 162.5, 325*, 650*, 1300*	4 hours	24 hours
Test 2	0*, 162.5, 325*, 650*, 1300*	4 hours	44 hours

*Cultures selected for micronucleus analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µL/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation in Main Test*	*Genotoxic Effect*
Absent				
Test 1	-	> 1,300	> 1,300	Negative
Test 2	-	> 1,300	> 1,300	Negative
Present				
Test 1	-	> 1,300	> 1,300	Negative
Test 2	-	> 1,300	> 1,300	Negative

Remarks - Results	The assessed chemical did not cause any increase in the number of cells carrying micronuclei in either the absence or presence of metabolic activation when tested up to the highest concentrations. The micronucleus rate of the treated cells was within the range of historical negative control data, although the highest concentration in Test 2 with metabolic activation was higher than the concurrent control and the 95% range of historical controls. However, the increase was not statistically significant. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system. In Test 1 without metabolic activation, EMS at 400 µg/mL gave a lower result than the historical controls. However EMS at 500 µg/mL gave a result within the historical controls, at the lower end.
CONCLUSION	The assessed chemical was not genotoxic to V79 cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BASF (2016b)

B.11. Genotoxicity – *in vitro* mammalian cell gene mutation test using the Thymidine Kinase Gene

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 490 *In vitro* Mammalian Cell Gene Mutation Test Using the Thymidine Kinase Gene (2016) EC Directive 2008/440/EC B.17 Mutagenicity – *In vitro* Mammalian Cell Gene Mutation Test

	US EPA OPPTS Guideline 870.5300 *In vitro* Mammalian Cell Gene Mutation Test
Species/Strain	Mouse
Cell Type/Cell Line	L5178Y mouse lymphoma cells ($TK^{+/-}$-3.7.2C)
Metabolic Activation System	S9-mix from phenobarbital (PB)/β-naphthoflavone (NF) induced rat liver
Vehicle	Culture medium
Remarks – Method	GLP certificate. A dose range-finding study was carried out at 5.5 – 1400 µg/mL (equivalent to 10 mM). No cytotoxicity or precipitation was observed in the presence and absence of the S9 mix. The dose selection for the main experiments was based on concentrations in the range-finding study. Vehicle and three positive controls (methyl methanesulfonate without metabolic activation), cyclophosphamide and 7,12-dimethylbenz[a]anthracene with metabolic activation) were run concurrently with the assessed chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0, 87.5, 175, 350, 700, 1400	4 hours	48 hours	9 – 10 days
Test 2	0, 87.5, 175, 350, 700, 1400	24 hours	48 hours	9 – 10 days
Present				
Test 1	0, 87.5, 175, 350, 700, 1400	4 hours	48 hours	9 – 10 days

All cultures were selected for mutation frequency (MF) 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	> 1,400	> 1,400	> 1,400	Negative
Test 2	≥ 1,400	> 1,400	> 1,400	Negative
Present				
Test 1	> 1,400	> 1,400	> 1,400	Negative

Remarks – Results	The assessed chemical did not lead to a statistically significant increase in the number of mutation frequencies at the TK-locus, either in the presence or absence of metabolic activation. The number of small and large colonies in treated cultures was within the range of the historical vehicle control data. Positive control values were within historical controls. The increase in the frequencies of mutant colonies induced by the positive control demonstrated the sensitivity of the test method and the metabolic activity of the S9 mix.
CONCLUSION	The assessed chemical was not mutagenic to mouse lymphoma cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BASF (2019)

B.12. Developmental Toxicity – Rat

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 414 Prenatal Developmental Toxicity Study (2018) US EPA OPPTS Guideline 870.3700 Prenatal Development Toxicity Study (1998)
Species/Strain	Rat/Wistar Crl:WI (Han)

Route of Administration	Oral – gavage
Exposure Information	Exposure days: 14 days (gestation days (GD) 6–19)
Vehicle	Corn oil
Remarks – Method	GLP compliant. No protocol deviations.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	25 F	0	0/25
Low Dose	25 F	15	0/25
Mid Dose	25 F	50	0/25
High Dose	25 F	150	0/25

Mortality and Time to Death

There were no deaths in any treated animals.

Effects on Dams

Within 2 hours after treatment, salivation occurred in dams, initially on GD 12 at 50 mg/kg bw/day and on GD 6 at 150 mg/kg bw/day.

Dams at ≥ 50 mg/kg bw/day showed adverse reductions in water and food consumption (17–24 % and 16–35 %, respectively), and corrected body weight gain (15– 27 % below control), as well as pathological changes of liver metabolism such as increases in cholesterol and triglyceride levels. Decreased total protein and albumin values were also reported at high dose.

In this study, the following parameters were reported to be within historical control data: conception rate, number of corpora lutea, implantations, pre-/post-implantation losses, resorptions and viable foetuses.

Effects on Foetus

Sex ratio, placental weight, and anogenital index of the foetuses were comparable to the controls following prenatal exposure (GD 6–19).

The mean foetal weights of the mid and high dose groups were statistically significantly reduced when the results for both sexes were combined (~ 6% and 8% below control, respectively). Fused placenta in one litter of each dose group treatment groups, but was considered within historical control levels. The incidence of branched rib cartilage was statistically significantly increased in the mid and high dose groups (2.4% and 1.9% affected foetuses per litter), but was reported to be within the historical control range.

Remarks – Results

The authors considered that the test substance was not teratogenic within the exposure window of GD 6–19.

CONCLUSION

The maternal NOAEL was established as 15 mg/kg bw/day in this study, based on the reduced water and food consumption, decreased body weight gain and pathological changes of liver metabolism observed in mid- and high-dose dams. The prenatal developmental NOAEL was established as 150 mg/kg bw/day by the study authors.

TEST FACILITY BASF (2020b)

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
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	TOC
Remarks – Method	No protocol deviation.

RESULTS

Test Substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
2	1	2	1
9	2	9	66
12	1	12	81
16	2	16	91
23	3	23	96
28	6	28	100

Remarks – Results	All validity criteria for the test were satisfied. Inorganic carbon in the mineral medium at the beginning of the test was < 5% of the total carbon. The CO_2 evolution in the control sample was less than 40 mg/L. The percentage degradation of the reference compound, aniline surpassed the threshold level of 60 % within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the assessed chemical after 28 days was 6%.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	BASF (2015g)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish - Static
Species	Zebrafish (*Danio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Limit test, carried out at 120 mg/L to ensure that the mean analytically measured concentration was above 100 mg/L.

RESULTS

Concentration (mg/L) *Nominal*	*Number of Fish*	*Mortality* *24 h*	*48 h*	*72 h*	*96 h*
0 (control)	7	0	0	0	0
120	7	0	0	0	0

LC50 > 120 mg/L at 96 hours

Remarks – Results All test concentrations were visibly clear over the entire exposure period and no undissolved material was observed. All validity criteria for the test were satisfied. According to OECD-guideline, the highest suggested test concentration is 100 mg/L for a limit test.

Dissolved oxygen was maintained at > 60% in all vessels. The pH of the solution was maintained between 7.5 and 8.5. Since the measured concentrations of the test substance in the test solutions were within ±20% of the nominal concentrations, the results are based on the nominal concentration of the test substance.

CONCLUSION The assessed chemical is not harmful to fish.

TEST FACILITY BASF (2015h)

C.2.2. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – static
EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia – static

Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 220 - 320 mg $CaCO_3$/L
Analytical Monitoring HPLC
Remarks – Method Limit test, carried out at 120 mg/L to ensure that the mean analytically measured concentration was above 100 mg/L. A positive control was run but details were not provided.

RESULTS

Concentration (mg/L) *Nominal*	*Number of D. magna*	*Number Immobilised* *24 h*	*48 h*
0 (control)	5	0	0
120	5	0	0

EC50 > 120 mg/L at 48 hours

Remarks – Results All test concentrations were visibly clear over the entire exposure period and no undissolved material was observed. All validity criteria for the test were satisfied. Oxygen content was maintained at ≥ 3 mg/L in all test vessels. The pH did not vary by more than 1.5 units and the temperature was maintained at 20 ± 1 °C. The reference test showed an EC50 value for sodium chloride of 4.06 mg/L which is within the expected range. According to OECD-guideline, the highest suggested test concentration is 100 mg/L for a limit test.

CONCLUSION	The assessed chemical is not harmful to aquatic invertebrates.
TEST FACILITY	BASF (2015i)

C.2.3. Algal Growth Inhibition Test

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 120 mg/L
Auxiliary Solvent	None
Remarks - Method	No protocol deviation. Potassium dichromate was used as a positive control reference substance, but details were not provided.

RESULTS

Biomass *EyC50* *mg/L at 72h*	*Growth* *ErC50* *mg/L at 72 h*
> 120	> 120

Remarks - Results	All test concentrations were visibly clear over the entire exposure period and no undissolved material was observed. All validity criteria were met. The growth factor in the control test was greater than 16. The coefficient of variation for section by section growth was 22.2% and the variation of average specific growth rate was 1.34%. Results from the positive control test was within the normal range for potassium dichromate (72 h EyC50 = 0.749 mg/L).
CONCLUSION	The test substance is not harmful to algal growth.
TEST FACILITY	BASF (2015j)

C.2.4. Inhibition of Microbial Activity

TEST SUBSTANCE	Assessed chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 7.8, 15.6, 31.3, 62.5 and 125 mg/L
Remarks – Method	No protocol deviation.
RESULTS	
IC50	110 mg/L
NOEC	> 110 mg/L
Remarks – Results	The coefficient of variation of the five replicates of blank control was 9.1 % O2 consumption. One of the validity criteria was not met. The mean oxygen uptake of the controls was 18 mg O_2/g of sludge, which is lower than the level specified in the validity criterion (20 mg O_2/g of sludge). Because the reference substance shows an EC50 in the specified range (usual range of EC50 of the last 20 values in the laboratory was 7.6 – 19.1 mg/L) and the measured oxygen uptake from the test substance concentrations showed a good curve progression the study is classified as valid.

	In addition the reference sample showed an EC50 for 3, 5-dichlorophenol of 13.2 mg/L which is within the expected range.
CONCLUSION	The test substance is not inhibitory to microbial respiration.
TEST FACILITY	BASF (2015k)

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