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September 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1-Butanamine, *N*-butyl-, reaction products with polyethylene glycol monoacrylate ether with trimethylolpropane (3:1)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Energy.

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

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

Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1586	BASF Australia Ltd	1-Butanamine, *N*-butyl-, reaction products with polyethylene glycol monoacrylate ether with trimethylolpropane (3:1)	Yes	≤ 40 tonnes per annum	Component of industrial paints and overprint varnishes

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Serious eye damage/eye irritation (Category 2A)	H319 – Causes serious eye irritation
Sensitisation, Skin (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):

R36: Irritating to eyes
R43: May cause skin sensitisation by skin contact

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

Hazard classification	*Hazard statement*
Acute Category 2	H401 – Toxic to aquatic life
Chronic Category 2	H411 – Toxic to aquatic life with long lasting effects

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

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

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Serious eye damage/eye irritation (Category 2A): H319 – Causes serious eye irritation
  - Sensitisation, Skin (Category 1): H317 – May cause an allergic skin reaction

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following isolation and engineering controls where possible to minimise occupational exposure to the notified chemical:
  - Enclosed and automated system during reformulation
  - Sufficient ventilation
  - Spray booth used for spray application where possible

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Protective clothing/coveralls
  - Impervious gloves
  - Eye protection
  - Respiratory protection during spray application

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

- Spray applications should be carried out in accordance with the Safe Work Australia Code of Practice for *Spray Painting and Powder Coating* (SWA, 2015) or relevant State or Territory Code of Practice.

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

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component of industrial paints and overprint varnishes, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12, 28 Freshwater Place
SOUTHBANK VIC 3006

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants, import volume, identity of manufacturer and identity of analogue.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for: hydrolysis as a function of pH, adsorption/desorption, dissociation constant, flammability, ready biodegradation, fish acute toxicity, daphnia acute immobilisation/reproduction and alga growth inhibition.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China, EU and Switzerland

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Laromer® LR 8869 (product containing 10-30% notified chemical)
Laromer® LR 8996 (product containing 10-30% notified chemical)
Laromer® LR 8996 M (product containing 10-30% notified chemical)

CAS NUMBER
195008-76-5

CHEMICAL NAME
1-Butanamine, *N*-butyl-, reaction products with polyethylene glycol monoacrylate ether with trimethylolpropane (3:1)

MOLECULAR WEIGHT
> 400 Da and < 1000 Da

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

3. COMPOSITION

DEGREE OF PURITY
The notified chemical is never isolated from the product mixtures. The product mixtures individually contain the notified chemical at 10-30% concentration.

4. PHYSICAL AND CHEMICAL PROPERTIES

Note: All measured physico-chemical properties were determined on the marketed product Laromer® LR 8869 containing 10-30% notified chemical and 70-90% Analogue 1 (identity in Exempt Information).

APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	Value	Data Source/Justification
Glass Transition Temperature	-71 °C	Measured
Boiling Point	Cannot be determined	Measured
Density	1,087.1 kg/m^3 at 20 °C	Measured
Viscosity	88.2 mm^2/s at 20 °C 29.7 mm^2/s at 40 °C	Measured
Vapour Pressure	1.9 × 10^{-1} kPa at 20 °C 2.4 × 10^{-1} kPa at 25 °C 7.2 × 10^{-1} kPa at 50 °C	Measured
Water Solubility	0.8 g/L at 1 g/L loading rate at 20 °C 2.3 g/L at 10 g/L loading rate at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ > 1 year at pH 4 $t_{½}$ = 352 days at pH 7 at 20 °C $t_{½}$ = 4.54 days at pH 9 at 20 °C	Measured (analogue data)
Partition Coefficient (n-octanol/water)	Log P_{OW} = 1.0-2.0 (peakgroup 1) Log P_{OW} = 2.5-3.5 (peakgroup 2)	Measured
Adsorption/Desorption	Not determined	Expected to adsorb to soil and sediment based on cationicity
Dissociation Constant	Not determined	Expected to be ionised under environmental conditions (pH 4-9)
Flash Point	> 110 °C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be highly flammable
Autoignition Temperature	370 °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 oxidative properties

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as a component of the marketed product mixtures (at 10-30% concentration) to be reformulated into industrial paints and overprint varnishes. In the future, the notified chemical may be imported into Australia as a component of finished industrial paints and overprint varnishes.

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

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

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
BASF Australia Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as a component of the marketed product mixtures (at 10-30% concentration) in 200 kg steel closed head drums and 1000 kg plastic/steel composite intermediate bulk containers by sea and then transported by road.

USE
The notified chemical will be used as a component of industrial paints and overprint varnishes.

OPERATION DESCRIPTION

Reformulation
The imported product containing the notified chemical at 10-30% concentration will be transferred to the paint or ink mixing tank by gravity feed or low pressure pumps. The product containing the notified chemical will be blended into a mixture of organic solvents in the mixing tank, with ventilation being expected to be in use. Following blending, the finished paints or overprint varnishes will be filled into steel containers through gravity feed or low pressure pumps. At the end of the reformulation process the equipment will be flushed with solvent for cleaning. Quality control staff may test samples of the finished products.

End-use
Finished paints or overprint varnishes will be applied by spray and industrial line roller, followed by UV or electron beam (EB) curing. Finished paints or overprint varnishes may be manually decanted and the subsequent application is expected to be automatic or semi-automatic through use of robotics, applicator-operated spray guns and industrial line roller.

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)*
Transportation and storage	1	4
Process operator	2-3	40
Quality control	1	40
Professional end-use	1	60

EXPOSURE DETAILS
Transport and storage workers are not expected to be exposed to the notified chemical except in the unlikely event of an accident.

Reformulation processes
Dermal, ocular and inhalation exposure to the notified chemical at concentrations up to 30% may occur when weighing, mixing and connecting or disconnecting transfer hoses, and during cleaning and maintenance of equipment. Exposure should be minimised through the use of enclosed and automated systems, local exhaust ventilation and personal protective equipment (PPE: goggles, impervious gloves, protective clothing and respirators during spray operations as recommended by the notifier).

Paint/varnish application
Dermal, ocular and inhalation exposure to the notified chemical (at ≤ 30%) may occur during spray or industrial line rolling applications of the finished paints and overprint varnishes, and when cleaning equipment. Exposure should be minimised through the use of automatic or semi-automatic processes (including robotics, applicator-

operated spray guns and industrial line roller), local exhaust ventilation and PPE (including goggles, impervious gloves, protective clothing and respirators as recommended by the notifier).

Once the paint or overprint varnish is dried and cured, the notified chemical will be bound into an inert solid matrix and will be unavailable for exposure.

6.1.2. Public Exposure

The finished products containing the notified chemical (≤ 30% concentration) will be used in industrial settings only and will not be made available to the public. Once the paint or overprint varnish is dried and cured, the notified chemical will be bound into an inert solid matrix and will be unavailable for exposure.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on an imported product mixture containing 10-30% notified chemical and 70-90% Analogue 1 (identity in Exempt Information) are summarised in the following table. As Analogue 1 is expected to have the same hazard profile as that of the notified chemical, the results from the studies conducted on the product mixture are assumed to reflect those of the notified chemical for risk assessment purposes. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, skin irritation	slightly irritating
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	irritating
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation (EC_3 = 1.5%)
Rat, repeat dose oral toxicity with reproductive/developmental screen	systemic NOAEL = 300 mg/kg bw/day reproductive/developmental NOAEL = 600 mg/kg bw/day local NOAEL = 100 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non-mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test	genotoxic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non-genotoxic

Toxicokinetics

No toxicokinetic data on the notified chemical were submitted. Based on the low molecular weight (> 400 Da and < 1000 Da), water solubility (0.8-2.3 g/L at 20 °C) and partition coefficient (log Pow = 1.0-3.5) of the notified chemical, absorption across biological membranes may occur.

Acute toxicity

The notified chemical is expected to have a low acute oral and dermal toxicity based on studies conducted in rats on the product mixture containing 10-30% notified chemical and 70-90% Analogue 1.

Irritation and sensitisation

The product mixture containing 10-30% notified chemical and 70-90% Analogue 1 was found to be slightly irritating or non-irritating to the skin in three studies conducted in rabbits. Based on weight of evidence, the product mixture is considered to be slightly irritating to skin.

The product mixture was found to be irritating to eyes in a study conducted in rabbits.

The product mixture containing 10-30% notified chemical and 70-90% Analogue 1 was found to be sensitising in a Local Lymph Node Assay. The EC_3 value was calculated to be 1.5%. It is noted that in this study there were indications of ear skin irritation, therefore an influence of irritation on lymphocyte proliferation cannot be excluded. Despite this, on the basis of the data, the study authors concluded that the test substance should be classified as a sensitiser. This is further supported by the presence of a structural alert for sensitisation in the notified chemical.

Repeated dose toxicity/Toxicity for reproduction
In a combined repeated dose oral (gavage) toxicity study with the reproduction/developmental toxicity screening test the product mixture containing 10-30% notified chemical and 70-90% Analogue 1 was administered to rats at 100, 300 and 1,000/600 mg/kg bw/day (reduced from 1000 mg/kg bw/day to 600 mg/kg bw/day from study day 19 onwards due to clinical findings and premature deaths of 2 female animals).

The systemic No Observed Adverse Effect Level (NOAEL) was established as 300 mg/kg bw/day in the study, based on premature deaths and clinical signs of systemic toxicity were noted at the higher dose level (1000/600 mg/kg bw/day).

The reproductive/developmental NOAEL was established as 600 mg/kg bw/day (the highest dose tested) based on no treatment-related adverse findings were noted at all doses tested.

The local NOAEL was established as 100 mg/kg bw/day based on local effects in the stomach noted at the higher dose levels (300 mg/kg bw/day and 1000/600 mg/kg bw/day). The pathological findings in the stomach at 300 mg/kg bw/day and above were considered by the study authors to be related to the irritating potential of the test substance.

Mutagenicity/Genotoxicity
The product mixture containing 10-30% notified chemical and 70-90% Analogue 1 was negative in a bacterial reverse mutation assay and negative in an *in vitro* mammalian cell gene mutation test in Chinese hamster ovary cells; however, the product mixture was positive in an *in vitro* mammalian cell gene mutation test in Chinese hamster V79 cells. When tested in an *in vivo* mammalian erythrocyte micronucleus test, the product mixture was negative, however there is no evidence that the test substance reached the bone marrow. Based on weight of evidence, the product mixture is expected to be non-genotoxic.

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

Hazard classification	***Hazard statement***
Serious eye damage/eye irritation (Category 2A)	H319 – Causes serious eye irritation
Sensitisation, Skin (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):

R36: Irritating to eyes
R43: May cause skin sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available information, the notified chemical is expected to be of low systemic toxicity, presenting as an eye irritant and a skin sensitiser.

Reformulation
During reformulation workers may be at risk of eye irritation and sensitisation when handling the notified chemical at ≤ 30% concentration. This risk should be minimised through the expected use of engineering controls such as enclosed, automated processes, spray booth, sufficient ventilation and personal protective equipment (PPE) including coveralls, impervious gloves, eye protection and respiratory protection.

Once the paints and varnishes have dried and cured, the notified chemical will be bound within the solid matrix and will not be available for exposure.

Therefore, provided that the recommended controls are being adhered to, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

The notified chemical will be used in industrial settings only and will not be made available to the public. Members of the public may come into contact with surfaces coated with products containing the notified chemical. However, once the paints and varnishes have dried and cured, the notified chemical will be bound within the solid matrix and will not be available for exposure.

Based on the assessed use patterns, the risk to the public from use of the notified chemical is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of a product for reformulation into finished UV/electron beam (UV/EB)-cured industrial paints and overprint varnishes. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical to the environment from this process is not expected. The reformulation process will be followed by automated filling of the formulated paints and overprint varnishes into containers suitable for distribution. Blending equipment will be cleaned with solvents, with waste liquids containing the notified chemical recycled during subsequent blending processes, or disposed of in accordance with local government regulations. Empty import containers are expected to be recycled or disposed of through licensed waste management services.

RELEASE OF CHEMICAL FROM USE

Finished UV/EB-cured paints containing the notified chemical will be applied by professional users only in industrial settings, for coating wood substrates. During use, industrial paints containing the notified chemical are expected to be applied by spray techniques or industrial rollers then UV/EB cured. The notified chemical is expected to be stable within an inert paint matrix on coated substrates once UV/EB-cured. Application of the paints is expected to occur within industrial facilities with ventilation systems to collect particulate overspray. Overspray and solid wastes from the application of paints containing the notified chemical will be collected, and disposed of in accordance with local government regulations, most likely to landfill. Residues containing the notified chemical in application equipment are expected to be cleaned with solvents, and then allowed to cure before disposal as solid wastes. During use, the notified chemical may also be released to the environment as accidental spills and container residues. These releases are expected to be collected and disposed of in accordance with local government regulations, most likely to landfill.

UV/EB-cured overprint varnishes containing the notified chemical will be applied in industrial settings only for printing onto paper substrates. It is estimated by the notifier that up to 25% of the import volume of the notified chemical (or up to 10,000 kg) will be used in overprint varnishes for printing onto paper substrates. Printing will largely occur within enclosed and automated systems. The notified chemical is expected to be stable within an inert coating matrix on paper substrates once UV/EB-cured. Potential environmental release of the notified chemical during use in overprint varnishes is expected to be limited to accidental spills and leaks. Spills and leaks are expected to be contained and collected with adsorbents, and disposed of in accordance with local government regulations, most likely to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

The majority of the notified chemical in industrial paints for wood substrates is expected to share the fate of the coated articles to which it is bound. These are predominantly expected to be disposed of to landfill at the end of their useful life. Empty paint containers are expected to be recycled or disposed of through licensed waste management services.

Of the 25% of the import volume of the notified chemical applied to paper, it is assumed that half of this amount is expected to be disposed of to landfill; the remainder is expected to undergo paper recycling processes. Empty containers are expected to be recycled or disposed of through licensed waste management services. Hence, the majority of the notified chemical in overprint varnishes is expected to be disposed of to landfill, with a potential for some release to sewer through paper recycling processes. During paper recycling processes, waste paper is repulped using a variety of chemical treatments which, amongst other things, will enhance varnish detachment from the fibres.

7.1.2. Environmental Fate

Following its use in UV/EB-cured industrial paints and overprint varnishes, the majority of the notified chemical is expected to be cured within an inert paint or varnish matrix, and is expected to remain adhered to the coated articles throughout its useful life. Once cured the notified chemical is not expected to be mobile, bioavailable, or bioaccumulative. The notified chemical is also expected to enter landfill as collected wastes and residues. Based on the results of a ready biodegradability study, the notified chemical is not considered to be readily biodegradable (24% in 28 days). For details of the environmental fate study, please refer to Appendix C. Release of the uncured notified chemical to surface waters is unlikely to occur, as the notified chemical is expected to adsorb to soil and sediment based on its cationicity. The uncured notified chemical is not expected to be bioaccumulative, due to its low partition coefficient (log K_{OW} = 1.0-2.0 and 2.5-3.5).

Approximately 50% of the paper substrates to which the ink containing the notified chemical is applied are expected to be recycled. During the de-inking process, the UV/EB cured ink containing the notified chemical is unlikely to be released into the supernatant waters. Based on its potentially cationic properties, the majority of the notified chemical is expected to adsorb to sludge and sediment. Sludge containing the notified chemical will eventually be disposed of to landfill, or re-used for soil remediation. Therefore, in landfill the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated based on the volume of the notified chemical in overprint varnishes to be applied to paper substrates (25% of the import volume, or 10,000 kg). It is expected that half of the paper products containing the notified chemical will be disposed of to landfill, and half will undergo recycling (i.e. half of 25% = 12.5% of the import volume). The PEC has been calculated assuming 96% removal of the notified chemical from influent during sewage treatment plants (STPs) processes through partitioning to sediment and sludge, based on the most conservative partition coefficient for the notified chemical (log P_{OW} = 1.0). As paper recycling is to be processed at facilities located throughout Australia, it is anticipated that such releases will occur over 260 working days per annum into the Australian effluent volume.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	40,000	kg/year
Proportion expected to be released to sewer	12.5%	
Annual quantity of chemical released to sewer	5,000	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	19.23	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	**96%**	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.213	µg/L
PEC - Ocean:	0.021	µg/L

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 6.38 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1,500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may be approximately 0.04 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10

years under repeated biosolids application, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 0.22 mg/kg and 0.43 mg/kg, respectively.

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 notified 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 0.21 µg/L may potentially result in a soil concentration of approximately 1.42 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 7.09 µg/kg and 14.17 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted for the notified chemical. The results from ecotoxicological investigations conducted on a close analogue substance (Analogue 1) were used to estimate the toxicity of the notified chemical. These results are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity	48 h EC50 = 70.7 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 = 2.2 mg/L	Toxic to algae
	72 h EC10 = 0.323 mg/L	Toxic to algae (chronic)
Inhibition of Bacterial Respiration	3 h IC50 > 1,000 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints for the analogue substance, and therefore the notified chemical, it is expected to be toxic to algae, and harmful to aquatic invertebrates. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as "Acute Category 2; Toxic to aquatic life". Based on the above chronic ecotoxicological endpoint and lack of ready biodegradability of the analogue substance, the notified chemical is formally classified as "Chronic Category 2; Toxic to aquatic life with long lasting effects" under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for algae. A safety factor of 250 was used given acute endpoints for two trophic levels and a chronic endpoint for algae are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC10 (Algae, 72 h)	0.323	mg/L
Assessment Factor	250	
Mitigation Factor	1.00	
PNEC:	1.29	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.213	1.29	**0.165**
Q – Ocean	0.021	1.29	**0.017**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. The notified chemical is not considered readily biodegradable; however it is expected to be ultimately biodegradable and is not expected to be bioavailable. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in industrial paints and overprint varnishes, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Glass Transition Temperature -71 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Determined by differential scanning calorimetry
Test Facility BASF (2013a)

Boiling Point Could not be determined

Method OECD TG 103 Boiling Point.
OECD TG 104 Vapour Pressure.
Remarks The boiling point was tried to be deduced from vapour pressure data obtained by the static method. However, extrapolation from the range of the measurement at 18.8 kPa to the normal boiling temperature at 101.3 kPa was not feasible as reliable data could not be extrapolated. The boiling point could therefore not be determined.
Test Facility BASF (2013a)

Density 1087.1 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Measured by oscillating densitometer
Test Facility BASF (2013a)

Viscosity 88.2 mm^2/s at 20 °C
29.7 mm^2/s at 40 °C

Method OECD TG 114 Viscosity of Liquids.
Remarks Determined by capillary viscometer
Test Facility BASF (2013a)

Vapour Pressure 1.9×10^{-1} kPa at 20 °C (extrapolated)
2.4×10^{-1} kPa at 25 °C (extrapolated)
7.2×10^{-1} kPa at 50 °C (measured)

Method OECD TG 104 Vapour Pressure.
Remarks Static method
Test Facility BASF (2013a)

Water Solubility 0.8 g/L at 1 g/L loading rate at 20 °C
2.3 g/L at 10 g/L loading rate at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method
Test Facility BASF (2013a)

Hydrolysis as a Function of pH $t_{½}$ > 1 year at pH 4
$t_{½}$ = 352 days at pH 7 at 20 °C
$t_{½}$ = 4.54 days at pH 9 at 20 °C

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)*	*$t_{½}$*
4	25	> 1 year
7	20	352 days
7	30	113 days
9	20	4.54 days
9	30	1.20 days

Remarks	The test was conducted on an analogue substance. After 5 days under the accelerated conditions of 50 °C the rate of hydrolysis of the notified chemical was less than 10% at pH 4. This equates to a half-life at 25 °C of $t_{½}$ > 1 year. The rate of hydrolysis of the notified chemical was 64% at pH 7 after 5 days, and reached 100% hydrolysis at pH 9. Therefore, it can be concluded that under the conditions of the test the analogue, and therefore the notified chemical, is expected to be hydrolytically stable under acidic conditions. The analogue, and therefore the notified chemical, is expected to hydrolyse slowly under neutral conditions, and is expected to hydrolyse rapidly under basic conditions.
Test Facility	Dr U Noack-Laboratorien (2010a)

Partition Coefficient (n-octanol/water)

Log P_{OW} = 1.0-2.0 (peakgroup 1)
Log P_{OW} = 2.5-3.5 (peakgroup 2)

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method
Test Facility	BASF (2013a)

Flash Point

> 110 °C at 101.3 kPa

Method	Similar to EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method
Test Facility	BASF (date not stated)

Autoignition Temperature

370 °C

Method	Similar to EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	BASF (date not stated)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	Olive oil DAB 9
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	2000	0/3
2	3M	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	No signs of toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	The animals showed the expected body weight gain.
CONCLUSION	The test substance is of low toxicity via the oral route.
TEST FACILITY	BASF (1993a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	None
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M, 5F	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Slight erythema was noted in 3 male animals on days 1 and 2. Well-defined erythema was noted in the other 2 male animals on days 1 and 2, with slight oedema on day 1. Slight erythema was noted in 3 female animals on study day 1 which increased to well-defined erythema on day 2. Well-defined erythema decreased to slight on day 6 in one of the 3 female animals, with incrustations noted on days 5-7. Well-defined erythema was noted in the 4th female animal on days 1-6, with slight oedema, incrustations and scaling also noted. Well-defined erythema was noted in the 5th female animal on days 1-2, with slight oedema noted on day 1.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	Male animals showed expected body weight gain. Body weight of female animals did not show significant change in week 1 but increased during week 2 within the normal range.

CONCLUSION	The test substance is of low toxicity via the dermal route.
TEST FACILITY	Bioassay (2011)

B.3. Irritation – skin

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/White Vienna
Number of Animals	3
Vehicle	None
Observation Period	8 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations. The test substance was applied in a single dose (0.5 mL) to the intact untreated skin of each animal.

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	1.3	1	0.3	2	< 8 days	0
Oedema	0	0	0	0	-	0

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

Remarks - Results	At the 24-hour observation, slight erythema was noted in two animals and well-defined erythema was noted in the remaining test animal. At the 48-hour observation irritation was resolved in one animal and slight erythema was noted in two animals which persisted to the 72-hour observation. All signs of irritation were resolved at the 8-day observation and the study was thus terminated. No signs of oedema were noted during the study.
CONCLUSION	The test substance is slightly irritating to the skin.
TEST FACILITY	BASF (1993b)

B.4. Irritation – skin

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	6M
Vehicle	None
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	No significant protocol deviations. The test substance (0.5 mL) was applied to a 6 cm^2 dry hydrophilic gauze pad which was applied to scarified and non-scarified skin sites of each animal. The test substance was held in place by means of an occlusive hypoallergenic dressing.

RESULTS
Non-scarified

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Erythema/Eschar	0.5	0.5	3	1	0.5	1	3	unknown	3

Oedema	0	0	0	0	0	0	0	-	0

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

Scarified

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Erythema/Eschar	0.5	0.5	3	2.5	2	1.5	3	unknown	3
Oedema	0	0	0	0	0	0	0	-	0

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

Remarks - Results

Non-scarified
Slight to marked erythema (Grade 1 to 3) was observed in all animals at the 24-hour observation. Marked Erythema (Grade 3) persisted in one animal only at the 72-hour observation.

Scarified
Slight to marked erythema was observed in all animals at the 24-hour observation. Erythema (Grade 1 to 3) persisted in 4 animals at the 72-observation.

No oedema was observed during the study. Reactions were in general of more severity on the scarified sites.

CONCLUSION

The test substance is slightly irritating to the skin.

TEST FACILITY

CIT (1995)

B.5. Irritation – skin

TEST SUBSTANCE

Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD

Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 6
Vehicle: None
Observation Period: 72 hours
Type of Dressing: Occlusive
Remarks - Method: No significant protocol deviations. The test substance (0.5 mL) was applied under a 25 mm × 25mm gauze pad to the intact and abraded skin sties on each animal.

RESULTS

Remarks - Results

The test substance did not cause any skin irritation at the 24-hour and 72-hour observations.

CONCLUSION

The test substance is non-irritating to the skin.

TEST FACILITY

HLS (1997)

B.6. Irritation – eye

TEST SUBSTANCE

Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD

OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 3
Observation Period: 8 days

Remarks - Method No significant 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	2.7	2.7	3	< 8 days	0
Conjunctiva: chemosis	0	1	1	2	< 8 days	0
Conjunctiva: discharge	0	1	1	2	< 72 hours	0
Corneal opacity	0	1	1	1	< 8 days	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results Conjunctival irritation was observed in all animals up to and including the 72-hour observation period. Corneal opacity (Grade 1) was observed in two animals at the 24-, 48- and 72-hour observation period. There were no signs of iridial inflammation. All signs of irritation were resolved at the 8-day observation and the study was thus terminated.

CONCLUSION The test substance is irritating to the eye.

TEST FACILITY BASF (1993c)

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

TEST SUBSTANCE Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/Ca
Vehicle Acetone/olive oil (4:1)
Preliminary study Yes
Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexyl cinnamaldehyde.
Remarks - Method No significant protocol deviations. Three preliminary tests were conducted on 2 female mice.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5F	412.0 ± 65.5	1.00
0.5%	5F	592.8 ± 135.7	1.44
0.6%	5F	769.6 ± 165.4	1.87
2.5%	5F	1757.8 ± 995.8	4.27

EC3 1.5%
Remarks - Results In first preliminary test, 2 animals treated with 50% and 100% test substance, respectively, showed erythema (both), swelling of the face (50%) and swelling of the ears/reduced spontaneous activity (100%). In the second preliminary test, 2 animals treated with 10% and 25% test substance, respectively, showed erythema (both), swelling of the ears (both), eschar formation (25%), an increase (> 25%) in ear weight and thickness (both). In the third preliminary test, 2 animals treated with 1% and 2.5% test substance, respectively, showed no signs of excessive local skin irritation or systemic toxicity.

In the main study, there were no deaths or signs of local skin irritation/ systemic toxicity observed in the test substance-treated or vehicle control

	animals. However, a statistically significant increase in ear weight was noted in the high dose group compared to the vehicle control group. Furthermore, the cutoff value for a positive response for the ear weight index of 1.1 for BALB/c mice was exceeded in this group. However the study author states that as the cutoff-value has been determined using a different strain of mice, it cannot be implicitly be adopted. The study author concludes that although an influence of irritation on lymphocyte proliferation cannot be excluded, the test substance has to be classified as a sensitiser.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance under the conditions of the test.
TEST FACILITY	Harlan (2012)

B.8. Repeat dose toxicity with reproduction/developmental toxicity screening

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 37 days (males)/52 days (females) Dose regimen: 7 days per week
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10 per sex	0	0/20
low dose	10 per sex	100	0/20
mid dose	10 per sex	300	0/20
high dose	10 per sex	1000/600*	2/20

* Reduced from 1000 mg/kg bw/day to 600 mg/kg bw/day from study day 19 onwards due to clinical findings and premature deaths of 2 female animals

Mortality and Time to Death

In the high dose group, 1 female animal and 1 male animal were found dead on mating day 3 and post-mating day 7, respectively. One female animal was sacrificed moribund on gestation day 2.

Clinical Observations

In the high dose group, piloerection was noted in 1 female animal during pre-mating and post-mating, and in 2 female animals in mating and gestation. Respiratory sounds were noted in 1 female animal during mating, in 2 female animals during gestation and in 1 female animal during lactation. Gasping was noted in 1 female animal during gestation and lactation. Smeared fur (in 1 female animal), poor general condition (in 2 female animals), hunched posture (in 1 female animal) and semi-closed eyelids (in 1 female animal) were noted during gestation.

No treatment-related, adverse findings were noted in the mid dose and low dose groups.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No treatment-related changes were noted in haematological parameters, clinical chemistry parameters or urinalysis parameters.

Effects in Organs

In the high dose group, erosion/ulcer was macroscopically noted in the forestomach of all male and 9 female

animals and microscopically noted in the forestomach of 5 male and 6 female animals. Slight to severe diffuse or focal hyperplasia with hyperkeratosis was noted in the forestomach of all animals, and slight to severe submucosal edema was noted in the forestomach of 8 male and 3 female animals.

In the mid dose group, erosion/ulcer was macroscopically noted in the forestomach of 3 male and 5 female animals and microscopically noted in the forestomach of 2 male and 2 female animals. Slight to severe diffuse or focal hyperplasia with hyperkeratosis was noted in the forestomach of 5 male and 7 female animals, and slight to severe submucosal edema was noted in the forestomach of 4 male and 6 female animals.

No treatment-related adverse findings were noted in the low dose group.

Reproductive performance
No treatment-related adverse findings were noted. Fertility and live birth indices were not affected.

Clinical examinations in F1 pups
No treatment-related adverse findings were noted. The viability index was not affected.

Remarks – Results
The pathological findings in the stomach at 300 mg/kg bw/day and above were considered by the study authors to be related to the irritating potential of the test substance.

CONCLUSION
The systemic No Observed Adverse Effect Level (NOAEL) was established as 300 mg/kg bw/day in this study, based on premature deaths and clinical signs of systemic toxicity noted at the higher dose level (1000/600 mg/kg bw/day).

The reproductive/developmental NOAEL was established as 600 mg/kg bw/day in this study, based on no treatment-related adverse findings were noted at all doses tested.

The local NOAEL was established as 100 mg/kg bw/day in this study, based on local effects in the stomach were noted at the higher dose levels (300 mg/kg bw/day and 1000/600 mg/kg bw/day).

TEST FACILITY BASF (2013c)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Product containing 10-30% notified chemical and 70-90% Analogue 1
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 0-5000 µg/plate b) Without metabolic activation: 0-5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No preliminary test was conducted. Positive controls: - With metabolic activation: 2-aminoanthracene (TA1535, TA1537, TA100, TA98, WP2uvrA) - Without metabolic activation: N-methyl-N'-nitro-N-nitrosoguanidine (TA1535, TA100); 4-nitro-o-phenylendiamine (TA98); 9-aminoacridine (TA1537); N-ethyl-N'-nitro-N-nitrosoguanidine (WP2uvrA)

RESULTS

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

Test 1	> 5000	> 5000	negative
Test 2	> 5000	> 5000	negative
Present			
Test 1	> 5000	> 5000	negative
Test 2	> 5000	> 5000	negative

Remarks - Results: No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

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

TEST FACILITY: BASF (1992)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE: Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD: OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.

Species/Strain: Chinese hamster

Cell Type/Cell Line: Ovary

Metabolic Activation System: S9 mix from phenobarbital/β-naphthoflavone induced rat liver

Vehicle: Dimethyl sulfoxide

Remarks – Method: A dose range-finding study was carried out at 0.39 – 100 µg/mL. The dose selection for the main tests was based on toxicity observed in the range-finding study.

Vehicle and positive controls (ethyl methanesulfonate and methylcholanthrene) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0.16*, 0.31*, 0.63*, 1.25*, 2.5*, 5, 10	4 h	7-9 days	6-7 days
Test 2	0.16, 0.31*, 0.63*, 1.25*, 2.5*, 5, 10	24 h	7-9 days	6-7 days
Present				
Test 1	3.13, 6.25*, 12.5*, 25*, 50*, 100, 150	4 h	7-9 days	6-7 days
Test 2	4.38*, 8.75*, 17.5*, 35*, 70*, 140	4 h	7-9 days	6-7 days

RESULTS

Metabolic Activation	*Test Substance Concentration (mM) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 3.13	> 1.25	> 100#	negative
Test 2	> 1.56	> 1.25	> 100#	negative
Present				
Test 1	> 50	> 50	> 100#	negative
Test 2	-	> 35	not reported	negative

Noted in the preliminary test

Remarks - Results: In both tests, the frequencies of revertant colonies were close to the range of the concurrent vehicle control values and within the range of the testing facility's historical negative control data.

A statistically significant dose-dependent increase in mutant colonies was noted in Test 2 in the absence of the metabolic activation. This finding however was not considered by the study authors to be biologically

relevant as all mutant rates were within the range of the testing facility's historical negative control data.

The results of the positive controls confirmed the validity of the test system.

CONCLUSION The test substance was not clastogenic to Chinese hamster ovary cells treated in vitro under the conditions of the test.

TEST FACILITY BASF (2012)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD OECD TG 487: In Vitro Mammalian Cell Micronucleus Test.

Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from β-naphthoflavone/sodium phenobarbitone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	A dose range-finding study was carried out at 39.1 – 5000 µg/mL. The dose selection for the main tests was based on toxicity observed in the range-finding study.

Vehicle and positive controls (ethyl methanesulfonate and cyclophosphamide) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Pre-test 1	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	4 h	24 h
Pre-test 2	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	24 h	24 h
Test 1	0.78, 1.56, 3.13, 6.25, 12.5, 25, 50	4 h	24 h
Test 2	0.13, 0.25*, 0.5*, 1*, 2, 4	4 h	24 h
Test 3	0.16, 0.31*, 0.63*, 1.25*, 2.5, 5	4 h	24 h
Present			
Pre-test 1	39.1, 78.1, 156.3, 312.5, 625, 1250, 2500, 5000	4 h	24 h
Test 1	1.56, 3.13, 6.25, 12.5*, 25*, 50*, 100	4 h	24 h
Test 2	7.5*, 15*, 30*, 60, 100	4 h	24 h
Test 3	5, 10*, 20*, 40*, 80	4 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Pre-test 1	< 39.1		> 78.1	
Pre-test 2	< 39.1		> 625	
Test 1		> 3.13	> 50	#
Test 2		> 2	> 4	positive
Test 3		> 5	> 5	positive
Present				
Pre-test 1	< 39.1		> 78.1	
Test 1		> 100	> 100	equivocal
Test 2		> 60	> 100	positive
Test 3		> 80	> 80	positive

The slides were not scorable due to low cell quality.

Remarks - Results

Without metabolic activation
In Tests 2 and 3 a dose dependant increase in the number of micronucleated cells was observed which were statistically significant at the highest dose.

With metabolic activation
In Test 1 the increase in the number of micronucleated cells of all doses were statistically significant compared with the vehicle control; however, the values were within the range of the historical negative controls.

In Test 2 a single intermediate dose (15 µg/mL) showed a weakly increased micronucleus rate. Due to inhomogeneous data and to corroborate this observation, increased samples of 4,000 cells per test group were scored at 15 and 30 µg/mL.

In Test 3 a dose dependant increase in the number of micronucleated cells was observed which was statistically significant at the highest dose.

Although the increases were only weak and the values were far below the concurrent positive control values, the findings were reproducible. Therefore, the findings were considered by the study authors to be of biological relevance.

The results of the positive controls confirmed the validity of the test system.

CONCLUSION

The test substance was clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test.

TEST FACILITY

BASF (2013b)

B.12. Genotoxicity – in vivo

TEST SUBSTANCE

Product containing 10-30% notified chemical and 70-90% Analogue 1

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/NMRI

Route of Administration: Oral – gavage

Vehicle: Corn oil

Remarks - Method: The selection of the highest dose for the main test was based on a preliminary study. Cytotoxicity was assessed by the ratio of polychromatic erythrocytes to total erythrocytes. Mutagenic response was indicated by the relevant increase of micronucleated PCEs.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control 1	5M	0	24 h
vehicle control 2	5M	0	48 h
low dose	7M	500	24 h
mid dose	7M	1000	24 h
high dose 1	7M	2000	24 h
high dose 2	7M	2000	48 h
positive control, CP	5M	40	24 h

CP = cyclophosphamide

RESULTS

Doses Producing Toxicity

No premature death occurred. Animals in all treatment groups showed no clinical signs of systemic toxicity.

There was no evidence of cytotoxicity in any treatment groups based on the comparison of relative PCE between treatment groups and negative

	control groups.
Genotoxic Effects	There were no statistically significant or biologically relevant increases in the frequency of micronucleated PCEs.
Remarks - Results	The positive and negative controls gave a satisfactory response confirming the validity of the test system. However, there is no indication that the test substance reached the bone marrow.
CONCLUSION	The test substance was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.
TEST FACILITY	Harlan (2013)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 301 A Ready Biodegradability: DOC Die-Away Test.
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved Organic Carbon (DOC)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Toxicity control*		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*	*Day*	*% Degradation*
7	17	7	54	7	89
14	13	14	55	14	90
21	12	21	61	21	91
28	24	28	60	28	101

Remarks – Results

All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 5 days (96%). Therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 5 days (55%; 60% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance.

The degree of degradation of the test substance after 28 days was 24%. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 A) guideline.

CONCLUSION

The analogue, and therefore the notified chemical, is not considered to be readily biodegradable.

TEST FACILITY

BASF (2004)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue 1
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	263-267 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L	*Number of D. magna*	*Cumulative Immobilised (%)*

Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
6.25	6.25	20	0	0
12.5	12.1	20	0	0
25.0	24.9	20	0	0
50.0	53.6	20	0	10
100	102	20	55	90

EC50	70.7 mg/L (95% CI 61.1-81.8 mg/L) at 48 hours
NOEC	50.0 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The actual concentrations of the test substance were measured at the start and end of the 48 h test period. As measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 48 h EC50 and NOEC for daphnids were determined to be 70.7 mg/L (95% CI 61.1-81.8 mg/L) and 50.0 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The analogue, and therefore the notified chemical, is considered to be harmful to aquatic invertebrates.
TEST FACILITY	Dr U Noack-Laboratorien (2010b)

C.2.2. Algal growth inhibition test

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test – Static.
Species	*Desmodesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 0.1-10 mg/L Actual: 0.0718-9.52 mg/L
Auxiliary Solvent	None
Water Hardness	0.24 mmol Ca + Mg/L
Analytical Monitoring	LC-MS/MS
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
0.437	0.0718	2.20	0.289

Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at the start and end of the 72 h test period. As measured concentrations deviated from the nominal concentrations by the end of the test, the geometric mean measured concentrations were calculated. The 72 h EC50 and NOEC for algae were determined to be 2.20 mg/L (95% CI 1.87-2.61 mg/L), based on geometric mean measured concentrations. The 72 h EC10 was determined to be 0.323 mg/L (95% CI 0.225-0.467 mg/L).
CONCLUSION	The analogue, and therefore the notified chemical, is considered to be toxic to algae.
TEST FACILITY	Dr U Noack-Laboratorien (2010c)

C.2.3. Inhibition of microbial activity

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 100-1,000 mg/L Actual: Not determined
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. Copper (II) sulphate pentahydrate was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.
RESULTS	
IC50	> 1,000 mg/L at 3 hours
NOEC	≤ 292 mg/L at 3 hours
Remarks – Results	All validity criteria for the test were satisfied. The 3 h IC50 and NOEC were determined to be > 1,000 mg/L and ≤ 292 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The analogue, and therefore the notified chemical, is not considered to be inhibitory to microbial respiration.
TEST FACILITY	Dr U Noack-Laboratorien (2010d)

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