File No: LTD/2071

May 2019

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Photoinitiator A18

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

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

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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
LTD/2071	Evonik Australia Pty Ltd and Brenntag Australia Pty Ltd	Photoinitiator A18	ND*	< 1 tonne per annum	Component of pressure sensitive adhesive tape

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
As only limited toxicity data on the notified chemical were provided, the notified chemical cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

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

Hazard Classification	*Hazard Statement*
Chronic (Category 1)	H410 - Very toxic to aquatic life with long lasting effect

Human Health Risk Assessment
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 reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated process where possible

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation processes:
  - Coveralls, impervious gloves, eye protection
  - Respiratory protection where aerosols are generated

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

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

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

Emergency procedures

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

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.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical;
  - the notified chemical is intended to be used in finished products at > 2% concentration.

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Evonik Australia Pty Ltd (ABN: 31 145 739 608)
Suite 33
1 Ricketts Road
MOUNT WAVERLEY VIC 3149

Brenntag Australia Pty Ltd (ABN: 84 117 996 595)
Level 5
10 Nexus Court
MULGRAVE VIC 3170

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year)

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are varied for hydrolysis as a function of pH, dissociation constant, explosive properties, oxidising properties and reactivity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU (2017)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Photoinitiator A18

MOLECULAR WEIGHT
< 500 g/mol

ANALYTICAL DATA
Reference NMR and FTIR spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Yellowish liquid

Property	*Value*	*Data Source/Justification*
Melting Point	None detected	Measured
Boiling Point	None detected	Measured; decomposition observed at > 275 °C
Density	945 kg/m^3 at 20 °C	Measured
Dynamic Viscosity	230 mPa.s	SDS
Vapour Pressure	5.69 × 10^{-7} kPa at 20 °C	Measured

Property	*Value*	*Data Source/Justification*
Water Solubility	0.764 – 1.53 × 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log P_{ow} > 6.5	Measured
Surface Tension	48.8 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 4.31 – 7.04	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	157 °C at 101 kPa	Measured
Flammability (in Contact with Water)	Not highly flammable	Estimated
Pyrophoric Properties	Not pyrophoric	Estimated
Autoignition Temperature	375 °C	Measured
Explosive Properties	Not explosive	Estimated
Oxidising Properties	Not oxidising	Estimated

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. The notified chemical is a photo initiator and may release free radical photo cleavage products under UV light. The notified chemical is also considered to be surface active based on the surface tension measured.

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported in a solution at > 90% concentration for formulation of pressure sensitive adhesive tapes.

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

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

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
Evonik Australia Pty Ltd
Brenntag Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical at > 90% concentration in a solution will be imported in 205 L drums. Locally manufactured finished products (pressure sensitive adhesive tapes) containing the notified chemical at ≤ 2% concentration will be packaged and transported as tape rolls for end-use applications.

USE
The notified chemical will be used at ≤ 2% concentration as a component of a siliconized liner in pressure sensitive adhesive tapes. The finished end-use products containing the adhesive tapes will be for industrial and domestic use.

End-use applications of the adhesive tapes may include:

Application Type	*Example*
Label	Standard labels, clear-on-clear labels, thermal labels and linerless labels
Personal hygiene products	Nappy (diaper) tapes and sanitary napkins
Building and insulation	Membranes, foams, floor covering, sound deadening and bitumen
Tapes	Industry, electronics, security, insulation, carpet and envelopes
Food packaging	Labels with indirect food contact
Other	Thermal transfer printing, over laminating, protective films, process liners and ceramic capacitors

OPERATION DESCRIPTION

The notified chemical imported at > 90% concentration will be used in the manufacture of a siliconized liner for use in pressure sensitive adhesive tapes.

At the manufacture site, the notified chemical at > 90% concentration will be manually decanted into a mixing vessel and mixed with other ingredients to produce silicon-liner mixture. The silicon-liner mixture containing the notified chemical at ≤ 2% concentration will be pumped to a coating machine using automated/semi-automated processes, added to substrate such as film or paper and UV-cured under closed and automated conditions. Adhesive will then be added to the substrate on top of the UV-cured silicon-liner within the same coating machine to form the end use tape. Converting steps such as die-cutting the end-use adhesive tape prior to adding it to consumer products may occur within the coating machine or separately.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and Warehousing	2 – 4	12
Mixing and Coating Machine operators	8	200
Maintenance workers	2 – 4	12

EXPOSURE DETAILS

Transport and storage workers may come into contact with the notified chemical (at > 90% concentration) only in the unlikely event of an accidental breach of the drums.

Manufacture of End Use Products

Incidental oral, dermal and ocular exposure to the notified chemical at > 90% concentration may occur during the manual connection and disconnection of taps (decanting step), when transferring the solution containing the notified chemical to the mixing vessel, and during equipment cleaning and maintenance. Given the low vapour pressure of the notified chemical, inhalation exposure is not expected unless aerosols are formed during the processes.

Manufacture of the adhesive tape will be largely enclosed and automated. However, workers may be exposed to the notified chemical at ≤ 2% concentrations during transfer processes, quality control testing, cleaning and maintenance.

Oral, dermal and ocular exposure to the notified chemical should be mitigated through the use of personal protective equipment (PPE) including protective coveralls, impervious gloves, goggles and a suitable respirator where local ventilation is not sufficient.

End Use

Workers may come into contact with the adhesive tape containing the notified chemical after manufacture. However, once the silicon liner has undergone UV-curing during the manufacture process, the notified chemical will be covalently bound onto the silicon-liner matrix and will not be available for exposure.

6.1.2. Public Exposure

The public may come into contact with the pressure sensitive adhesive tapes containing the notified chemical after application to end-use products. However, once the silicon-liner (containing the notified chemical at ≤ 2% concentration) has been UV-cured within the coating machine, the notified chemical will be covalently bound onto the substrate matrix and will not be available for exposure.

The notifier provided certification describing how silicon acrylate products containing the notified chemical meet the relevant European Union migration requirements for use as release coatings for plastic film grades and paper grades applicable in the field of food packaging and labelling, and as release coating for film grades and paper grades which serve as adhesive tapes for use in the hygiene sector (ISEGA 2018).

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*	*Test Substance*
Acute oral toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity	analogue chemical
Acute dermal toxicity – rat	LD50 > 2,000 mg/kg bw; low toxicity	notified chemical
Skin irritation – rabbit	slightly irritating	analogue chemical
Eye irritation – *in vivo* HET-CAM*	slightly irritating	analogue chemical
Eye irritation – rabbit	slightly irritating	analogue chemical
Skin sensitisation – guinea pig, maximisation test	evidence of sensitisation (positive response was observed in 20% of animals)	analogue chemical
Repeat dose oral toxicity – rat, 28 days	NOAEL – 300 mg/kg bw/day	notified chemical
Mutagenicity – bacterial reverse mutation	non mutagenic	analogue chemical
Genotoxicity – *in vitro* Chromosome Aberration Test	non clastogenic	notified chemical
Genotoxicity – *in vitro* Mammalian Cell Gene Mutation Test	non mutagenic	notified chemical

* HET-CAM: Hen's Egg Test – Chorioallantoic Membrane

The analogue chemical shares similar structural features as the notified chemical and is expected to have a similar physicochemical and toxicological profile to that of the notified chemical. Data on the analogue were used to estimate the acute toxicity, irritation properties, skin sensitisation and genotoxicity of the notified chemical.

Toxicokinetics, Metabolism and Distribution

No information on the toxicokinetics of the notified chemical was provided. For dermal absorption, molecular weights below 500 g/mol are favourable for absorption and molecular weights above 1,000 g/mol do not favour absorption (ECHA, 2017). Dermal uptake is likely to be low to moderate if the water solubility is between 1-100 mg/L. Dermal uptake through the epidermis is expected if the partition coefficient (log P_{ow}) of the chemical is between -1 and 4 (ECHA, 2017). In this log P_{ow} range, gastrointestinal absorption and absorption across the respiratory tract are also likely to be high. Absorption of the notified chemical through the skin, gastrointestinal tract and respiratory tract is expected to be limited based on the low water solubility (< 1.53 mg/L) but is likely to occur due to the low molecular weight (< 500 g/mol). The high partition coefficient (log P_{ow} > 6.5) may limit the rate of transfer between the stratum corneum and epidermis mitigating dermal penetration of the notified chemical.

Acute Toxicity

The notified chemical was of low acute toxicity by the dermal route with LD50 > 2,000 mg/kg bw based on a study conducted in rats. It is also expected to be of low acute toxicity via the oral route based on a study conducted in rats using the analogue chemical.

Irritation

Based on studies in rabbits conducted on the analogue, the notified chemical is expected to be slightly irritating to the skin and eyes.

Sensitisation
The notified chemical may have skin sensitisation potential based on the skin reactions observed following exposure of test animals to an analogue chemical. The analogue showed evidence of skin sensitisation in a Guinea Pig maximisation test with an intradermal induction concentration of 5%, topical induction concentration of 75% and at a challenge concentration (topical application) of 60%. The sensitisation rate was determined to be 20% (as observed in 2 of 10 animals) and therefore the results did not warrant a skin sensitisation classification under the GHS criteria.

Repeated Dose Toxicity
In a 28 day repeat dose oral gavage study, rats were administered the notified chemical at 30, 100 and 300 mg/kg bw/day.

Total bilirubin levels were statistically significantly decreased in males and females exposed to the highest dose when compared to the controls. Increased cholesterol levels were observed in females, with animals exposed to the highest dose exhibiting statistical significance. Increased liver weights were observed in males and females exposed to mid- and high-doses of the notified chemical. There were no associated microscopic findings recorded. These effects were therefore considered by the study authors to be of minor nature within or marginally outside the normal range and to be of no toxicological significance.

The No Observed Adverse Effect Level (NOAEL) for the notified chemical is established as 300 mg/kg bw/day in this study as no toxicologically significant adverse effects were reported at the highest dose tested.

Mutagenicity/Genotoxicity
The notified chemical was non-genotoxic in an in vitro mammalian chromosome aberration test using peripheral lymphocytes and an in vitro mammalian cell mutation study using Chinese Hamster V79 cells. The notified chemical is not expected to be mutagenic based on a bacterial reverse mutation study performed on the analogue chemical.

Health Hazard Classification
As only limited toxicity data on the notified chemical were provided, the notified chemical cannot be classified according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS), as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on studies on an analogue chemical, the notified chemical may have the potential to be slightly irritating to the skin/eyes or a weak skin sensitiser. Therefore, control measures are required to mitigate possible adverse health effects to the workers who may come into contact with the notified chemical.

Manufacture of End Use Products (Reformulation)
Exposure of workers to the notified chemical (at > 90% concentration) may occur during transferring and blending operations. Provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End Use
Workers will come into contact with the notified chemical at ≤ 2% concentration that is expected to be covalently bound to the silicon liner matrix. The risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

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

6.3.2. Public Health
Members of the public may come into contact with the notified chemical at ≤ 2% concentration through the use of adhesive tapes containing the notified chemical. The main route of exposure is expected to be dermal. However, once the silicon-liner containing the notified chemical has been UV-cured within the coating machine,

the notified chemical will be covalently bound onto the substrate matrix and is not expected to be available for exposure.

The main potential risk associated with the use of the notified chemical in adhesive tapes is the potential for slight skin/eye irritation and weak skin sensitisation based on studies conducted on the analogue chemical. The skin or eye effects of the notified chemical were observed only at high concentrations.

End use adhesive tapes containing the notified chemical at ≤ 2% concentration may be used in applications with indirect food contact such as labels or in hygiene products such as sanitary napkins and nappies (diapers). Given the low concentration in these end-use products, the risk to public health is not considered 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 in a solution for formulation of finished adhesive tapes. Any waste generated during the formulation process is expected to be disposed of in accordance with local government regulations. Accidental spills of the product containing the notified chemical during import, transport, storage or formulation are expected to be absorbed onto suitable materials and collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE
Once the silicon liner has been cured, the notified chemical will be bound within the matrix and will not be available for release.

RELEASE OF CHEMICAL FROM DISPOSAL
Residual notified chemical in empty containers will be disposed of with the containers to landfill.

7.1.2. Environmental Fate
Biodegradation tests conducted on the notified chemical show that it is not readily biodegradable but inherently biodegradable. For details of the biodegradation tests, see Appendix C.

Most of the notified chemical will share the fate of the adhesive tapes and be disposed of to landfill at the end of their use lives. In landfill, the notified chemical will present as cured solids and will neither be bioavailable nor mobile. The notified chemical is expected to eventually degrade via biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)
The predicted environmental concentration (PEC) has not been calculated as release of the notified chemical to the aquatic environment will be limited based on its reported use pattern.

7.2. Environmental Effects Assessment
Results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Acute Fish Toxicity	96 hours LC50 > 100 mg WAF*/L	Not harmful to fish up to its water solubility limit
Early Life-Stage Fish Toxicity	32 days NOEC = 59 µg/L 32 days LOEC > 59 µg/L	Does not affect fish early life-stage
Acute Daphnia Toxicity	48 hours EC50 > 100 mg WAF*/L	Not harmful to Daphnia up to its water solubility limit
Chronic Daphnia Toxicity	21 days EC50 = 54 µg/L 21 days NOEC = 26 µg/L	Very toxic to Daphnia with long lasting effects
Algal Toxicity	96 hours EC50 > 100 mg WAF*/L	Not harmful to alga up to its water solubility limit

Endpoint	*Result*	*Assessment Conclusion*
Inhibition of Bacterial Respiration	3 hours IC50 > 100 mg/L	Not inhibitory to microbial respiration at STPs

* WAF: Water Accommodated Fraction

Under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), the notified chemical is expected to be very toxic to aquatic life with long lasting effects. Therefore, the notified chemical is formally classified as "Chronic Category 1; Very toxic to aquatic life with long lasting effects" under the GHS (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration (PNEC)

The most sensitive endpoint from the above ecotoxicity tests is 21 days NOEC for Daphnia, and this was selected for the calculation of the predicted no-effect concentration (PNEC). An assessment factor of 25 was used in this case given acute endpoints for three trophic levels and chronic endpoints for two trophic levels are available as a general indication of potential toxicity.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
21 days NOEC to Daphnia	26	µg/L
Assessment Factor	25	
Mitigation Factor	1.00	
PNEC	1.04	µg/L

7.3. Environmental Risk Assessment

The risk quotient (Q = PEC/PNEC) for the notified chemical has not been calculated as release to the aquatic environment in ecotoxicologically significant concentration is not expected based on its reported use pattern. Therefore, on the basis of this assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point None detected

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	A small glass transition peak was observed between -50 °C and -70 °C. No transition from a solid to liquid state was observed.
Test Facility	NOTOX (2008a)

Boiling Point None detected

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	An endothermic effect was observed at temperatures above 275 °C indicative of reaction or decomposition of the test substance. A yellow/brown coloured residue was observed at the end of the experiment (at 349 °C).
Test Facility	NOTOX (2008a)

Density 945 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Pycnometer method
Test Facility	NOTOX (2008a)

Vapour Pressure 5.69×10^{-7} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Isothermal thermogravimetric effusion method
Test Facility	NOTOX (2008a)

Water Solubility $0.764 – 1.53 \times 10^{-3}$ g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method (although the water solubility is < 10^{-2} g/L)
Test Facility	NOTOX (2008a)

Partition Coefficient (n-octanol/water) $\log P_{ow} > 6.5$

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method; the test substance is surface-active.
Test Facility	NOTOX (2008a)

Surface Tension 48.8 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	Concentration: 90% of saturation in water Ring method
Test Facility	NOTOX (2008a)

Adsorption/Desorption $\log K_{oc} = 4.31 – 7.04$

Method	OECD TG 121 Estimation of the Adsorption Coefficient on Soil and on Sewage Sludge

Using HPLC Method
EC Council Regulation No 440/2008 C.19 Estimation of the Adsorption Coefficient on Soil and on Sewage Sludge Using HPLC Method

Remarks The test substance is a mixture of isomerised homologues.
Test Facility NOTOX (2009a)

Flash Point 157 °C at 101.3 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point
Remarks Pensky-Martens Closed Cup method
Test Facility NOTOX (2008a)

Flammability (in Contact with Water) Not highly flammable

Method EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water)
Remarks The study authors stated that the chemical structure contains no functional groups that would imply the evolution of flammable gas(es) when in contact with water. No metals, boron or silicon are present.

The impurities were not considered by the study authors as they were not expected to have any influence on the chemical's flammability. No interaction between the different components is expected to occur.
Test Facility NOTOX (2008a)

Pyrophoric Properties Not pyrophoric

Method EC Council Regulation No 440/2008 A.13 Pyrophoric Properties of Solids and Liquids
Remarks The study authors stated that the chemical structure contains no functional groups that would imply the spontaneous ignition of the chemical following contact with air.

The impurities were not considered by the study authors as they were not expected to have any influence on the chemical's flammability.
Test Facility NOTOX (2008a)

Autoignition Temperature 375 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks Commercial auto-ignition temperature apparatus
Test Facility NOTOX (2008a)

Explosive Properties Not explosive

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks The study authors stated that the chemical contains no functional groups that would imply explosive properties. The calculated oxygen balance for the notified chemical is outside the range of values that would indicate a potential for explosiveness.
Test Facility NOTOX (2008a)

Oxidizing Properties No oxidising properties

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks The study authors stated that the chemical contains no functional groups that would imply oxidising properties. The oxygen atom present is bonded to carbon indicating the molecule is oxygen deficient.

The impurities were not considered by the study authors as they were not expected to have any influence on the chemical's oxidising potential.
Test Facility NOTOX (2008a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Wistar
Vehicle	Sesame oil
Remarks – Method	GLP compliant. No significant deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 M	200	0/3
2	3 M, 3 F	2,000	0/6

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No signs of toxicity observed
Effects in Organs	No macroscopic abnormalities detected
Remarks – Results	All animals made the expected body weight gains.

CONCLUSION	The test substance is of low acute toxicity via the oral route.
TEST FACILITY	Degussa (2004a)

B.2. Acute Dermal Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/CD/Crl: CD(SD)
Vehicle	None
Type of dressing	Occlusive
Remarks – Method	GLP compliant No significant deviations from the protocol

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity – Local	No signs of toxicity observed. No skin reactions were observed at the application site.
Signs of Toxicity – Systemic	No signs of toxicity observed
Effects in Organs	No macroscopic abnormalities detected
Remarks – Results	All animals made the expected body weight gains.

CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	LPT (2014)

B.3. Skin Irritation – Rabbit

TEST SUBSTANCE	Analogue chemical

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (1 M, 2 F)
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks – Method	GLP compliant No significant deviations from the protocol

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.67	0.33	0	0	< 72 hours	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	Following removal of the test substance, the female animals exhibited slight erythema at 1 hour and 24 hours, persisting in one animal up to the 48 hour observation. Both animals exhibited full recovery at the 72 hour observation. One animal exhibited skin peeling (desquamation) 7 days after exposure, with recovery indicated (decrease in the effect) by day 14 of the study period. No effects were observed in the male animal over the course of the study. No signs of oedema were observed in any of the animals. All animals made the expected body weight gains. No signs of systemic toxicity were observed.
CONCLUSION	The test substance is slightly irritating to the skin.
TEST FACILITY	Degussa (2004b)

B.4. Eye Irritation – *In Vitro* HET-CAM

TEST SUBSTANCE	Analogue chemical
METHOD	The Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) method used is based on publications by Prof. Dr. N.-P. Lüpke, Institute for Pharmacology and Toxicology, University of Münster.
Vehicle	None
Remarks – Method	Nine days after the fertilized eggs (SPAFAS strain) were added to the incubator, the shell over the air sac of each egg was removed. The inner egg membrane sack was wetted with physiological saline and the inner egg membrane removed to reveal the CAM. Eggs with small lesions or haemorrhages after preparation were rejected. A 200 µL sample of the test substance was applied onto the CAM of two eggs and blood vessels of the CAM were continuously observed for the 5 minute observation period. Untreated areas of the egg served as control. The test was repeated three times (total of 6 eggs tested). Six (6) positive and 6 negative controls were also included in the study. All CAMs were exposed to the test substance or control for the length of the observation period (5 min). Observations were made at 0.5, 2 and 5 min post-application.

The reactions of the CAM, were examined and the following scoring scheme for irritant effects were applied as described below:

Effect	*Scores at time (min)*		
	0.5	2	5
Vascular injection	5	3	1
Haemorrhage	7	5	3
Coagulation	9	7	5

Each reaction was recorded only once for each CAM. Scoring was based on the severity and time needed for the effect to occur. The severity of the effects was ordered as follows: coagulation > haemorrhage > vascular injection.

The recorded scores for every possible reaction were summed for each egg, with the average score for the tested eggs corresponding to the irritation index of the test substance. This was then used to classify in analogy to the Draize eye irritation test as described below:

Irritation index	*Classification*
0 – 0.9	not irritating
1 – 4.9	slightly irritating
5 – 8.9	moderately irritating
9 – 21.0	strongly irritating

Positive control: 5% Texapon ASV (sodium magnesium lauryl-myristyl-6-ethoxy-sulfate)
Negative control: Tap water

The testing laboratory was GLP compliant.

RESULTS

Test substance	*Total score*	*Number of sample*	*Average score (irritation index)*
Negative control	0	6	0
Test substance	25	6	4.2
Positive control	56	6	9.3

Remarks – Results

Vascular injection of the CAM was observed in two eggs 0.5 min after exposure, and in the remaining four eggs 2 min after exposure. Haemorrhage of one egg was observed 5 min after exposure

Positive and negative controls performed as expected.

CONCLUSION

The test substance is predicted to be slightly irritating to the eye under the conditions of the test.

TEST FACILITY

Degussa (2004c)

B.5. Eye Irritation – Rabbit

TEST SUBSTANCE

Analogue chemical

METHOD

OECD TG 405 Acute Eye Irritation/Corrosion
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation)

Species/Strain: Rabbit/New Zealand White
Number of Animals: 3 (1 M, 2 F)
Observation Period: 7 days
Remarks – Method: GLP compliant.

No significant deviations from the protocol.

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	0	0	0	1	< 24 hours	0
Conjunctiva – Chemosis	0	0	0	1	< 24 hours	0
Conjunctiva – Discharge	0	0	0	0	-	0
Corneal Opacity	0	0	0	0	-	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

Slight conjunctival redness and chemosis were observed in all animals one hour after exposure. Full recovery was observed in all animals at the 24 hour observation and over the course of the observation period.

One male and one female made the expected body weight gains. One female exhibited a body weight loss of 4.6% which the study authors did not attribute to the test substance, but suggested it might have been due to competition for food between the two females who were housed together. This female was heavier at the start of the study, but exhibited a similar body weight to the other female at the end of the study. The study authors did not consider the drop in body weight to have a negative impact on the results of the study.

No signs of systemic toxicity were observed.

CONCLUSION The test substance is slightly irritating to the eye.

TEST FACILITY Degussa (2004d)

B.6. Skin Sensitisation – Guinea Pig, Maximisation Test

TEST SUBSTANCE Analogue chemical

METHOD OECD TG 406 Skin Sensitisation – Maximisation Test

Species/Strain Guinea pig/Pirbright White

PRELIMINARY STUDY Maximum non-irritating concentration:
Intradermal: 1.0%; very slight erythema observed at 2.5% and 5%
Topical: 60%; very slight erythema observed at 75%

MAIN STUDY

Number of Animals Test Group: 10 Control Group: 5

Vehicle Sesame oil

Positive Control 2-mercaptobenzothiazole

INDUCTION PHASE Induction concentration:
Intradermal: 5%
Topical: 75%

Signs of Irritation Intradermal: very slight erythema, but no oedema, was observed in all animals exposed to the test substance. No reactions were observed in animals in the control group. Crust formation was observed at injections sites applied with Freund's Complete Adjuvant (FCA) (test group and control).

Topical: very slight erythema was observed in 4/10 animals exposed to the test substance. No signs of oedema were observed in any of the animals exposed to the test substance. No reactions were observed in animals in the control group.

CHALLENGE PHASE

1st Challenge	Topical: 60%
2nd Challenge	Not conducted
Remarks – Method	GLP compliant No deviations from the protocol Topical applications were applied under occlusive dressing

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after Challenge*	
		24 h	*48 h*
Test Group	60%	2/10	2/10
Control Group	60%	0/5	0/5

Remarks – Results

Very slight erythema was observed in one animal and very slight oedema was observed in a second animal throughout the challenge phase (observations made 24 and 48 hours following exposure). No other signs of toxicity or ill health were observed. All animals made the expected body weight gains.

The sensitisation rate was determined to be 20%.

No adverse effects were recorded in animals in the control group.

The positive control performed as expected, producing a sensitisation rate of 70%.

CONCLUSION

There was evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.

TEST FACILITY

Degussa (2004e)

B.7. Repeat Dose Oral Toxicity – Rat

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral)

Species/Strain	Rat/Wistar/SPF
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Polyethylene glycol
Remarks – Method	GLP compliant There were no deviations from the protocol

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5 F, 5 M	0	0
Low Dose	5 F, 5 M	30	0
Mid Dose	5 F, 5 M	100	0
High Dose	5 F, 5 M	300	0

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

There were no clinical signs of toxicity.

Slight salivation following dosing was observed in 1/5 males in the control group, 1/5 males in low-dose

groups, and all males in the mid- and high-dose groups. Slight to moderate salivation was observed in 4/5 females in the low-dose group and all females in the mid- and high-dose groups. Animals in the control, low-, and mid-dose groups exhibited salivation within the last ten days of the experimental period, whereas animals in the high-dose groups exhibited salivation intermittently throughout the experimental period. The study authors considered this effect to be a physiological response rather than a sign of systemic toxicity.

Slight to moderate scabbing was observed on the right shoulder of 1/5 males in the high-dose group over days 20 to 25 of the study period. The effect was not observed in any other animals. The study authors stated that this effect occurred within the range of background findings and was not considered a sign of toxicological significance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No significant differences in haematology were observed between rats exposed to the test substance and those in the control group.

One female in the low-dose group exhibited lower red blood cell counts, higher relative reticulocyte counts, higher red blood cell distribution width, lower haemoglobin levels and a lower haematocrit value. The same combination was not observed in other animals. The study authors did not consider the observation to be of toxicological significance or related to exposure to the test substance.

Percentage of reticulocytes in females increased in a dose-response relationship across the low-, mid- and high-dose groups. These differences were not statistically significant and the pattern was not observed in males.

Aspartate aminotransferase (ASAT) levels increased in males in all dosed groups when compared to the control group. These differences were not statistically significant and the pattern was not observed in females.

Levels of bile acid and potassium in males decreased in a dose-response relationship with the high-dose males display statistically significance when compared with the controls. This effect was not observed in females. The study authors considered this effect to be due to high levels of bile acid in the control males. Levels of bile acid in females increased across the low-, mid- and high-dose groups in a dose-response manner. As there was no correlation between males and females, the effect was not considered by the study authors to be of toxicological significance.

Total bilirubin levels in males decreased in a dose-response manner across the low-, mid- and high-dose groups. The total bilirubin levels in high-dose males and females were statistically significantly lower than the levels observed in the controls.

Alkaline phosphatase (ALP) levels in females decreased across the low-, mid- and high-dose groups in a dose-response manner when compared to controls. These values were not statistically significantly lower than the controls.

Glucose levels in females decreased in a dose-response manner across the low-, mid- and high-dose groups. Higher glucose levels in males were observed in the low- and mid-dose groups. However, these changes were not statistically significant when compared to the controls.

Cholesterol levels in females increased in a dose-response manner across the low-, mid- and high-dose groups with the high-dose group showing statistical significance.

Effects in Organs

No toxicologically relevant alterations were observed at the macroscopic level.

Incidental findings in females of all groups included fluid in uterus (4/5, 3/5, 1/5 and 2/5 in the control-, low-, mid- and high-dose groups respectively), isolated reddish foci on the glandular mucosa of the stomach (1/5, low-dose group), dark red foci on the thymus (1/5, low-dose group), tan discolouration of the clitoral glands (1/5, mid-dose group) and a yellowish hard nodule on the left mandibular lymph node (1/5, high-dose group). The study authors reported that these findings are occasionally seen in rats used in these types of studies and were considered of no toxicological importance.

The liver weights of some animals were increased (mid- and high-dose groups), but only marginally outside the range considered normal for rats of this age and strain. In the absence of supporting macroscopic or microscopic

findings, the changes were not considered to be of toxicological importance.

Statistically significantly higher thyroid weights in males in the mid-dose group were reported but the study authors reported that these were within the normal range for rats of this age and strain, and were only marginally different when compared to controls.

In females, thymus weights and thymus to body weight ration decreased and heart weight and heart to body weight ratios increased (not statistically significant) across all groups in a dose-response manner compared to the controls.

The study authors considered that all microscopic observations were within the range of background pathology for rats of this age and strain.

Remarks – Results

Males in the high-dose group exhibited slightly lower body weights and body weight gain compared to males in the control group. The difference was not statistically significant and the values were within the historical range for animals of this age and strain. All other animals made the expected body weight gains.

No clinical signs of toxicity were observed. No significant differences in haematology were observed between rats exposed to the test substance and those in the control group. Some clinical chemistry changes (see above) were recorded; however as these effects were not always significantly different to the controls, only occurred in one sex, or were within the historical range for animals of this age and strain, the study authors did not consider them to be of toxicological significance or related to exposure to the test substance.

All macroscopic and microscopic observations (see above) were not considered to be of toxicological importance as they were not always significantly different to the controls, were either within or only marginally outside the range considered normal for rats of this age and strain, only occurred in one sex, and were not supported by other clinical or haematological changes.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 300 mg/kg bw/day in this study, based on no toxicologically relevant adverse effects at the highest dose tested.

TEST FACILITY	NOTOX (2009b)

B.8. Genotoxicity – Bacteria

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test	Test 1: a) With metabolic activation: 313 – 5,000 µg/plate b) Without metabolic activation: 313 – 5,000 µg/plate Test 2: a) With metabolic activation: 125 – 1,000 µg/plate b) Without metabolic activation: 125 – 1,000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks – Method	GLP compliant No significant protocol deviations No preliminary toxicity test was performed. Test 1 acted as a preliminary test. Positive controls: Without metabolic activation – Sodium azide (TA100, TA1535), 9-

Aminoacridine (TA1537), 4-Nitrofluorene (TA98), Mitomycin C (TA102);
With metabolic activation – 2-Aminoanthracene (TA100, TA1535, TA1537, TA102), Benzo[a]pyrene (TA98).

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*		
	Cytotoxicity	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 5,000 μg/plate	≥ 1,250 μg/plate	negative
Test 2	> 5,000 μg/plate	> 1,000 μg/plate	negative
Present			
Test 1	> 5,000 μg/plate	≥ 1,250 μg/plate	negative
Test 2	> 5,000 μg/plate	> 1,000 μg/plate	negative

Remarks – Results

No significant increases in the frequency of revertant colonies were recorded for any of the strains at any concentration either with or without metabolic activation.

Precipitation was observed at concentration ≥ 1250 μg/plate in test 1 and was not observed at any concentration in test 2 up to 1,000 μg/plate.

All of the positive control chemicals used in the test induced significant increases in the frequency of revertant colonies with or without metabolic activation, confirming the sensitivity of the strains and activity of the S9-mix.

CONCLUSION

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

TEST FACILITY

Degussa (2004f)

B.9. Genotoxicity – *In Vitro* Mammalian Chromosome Aberration Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
EC Directive 2000/32/EC B.10 Mutagenicity – *In vitro* Mammalian Chromosome Aberration Test

Species/Strain: Human cells
Cell Type/Cell Line: Peripheral lymphocytes
Metabolic Activation System: S9 fraction from phenobarbital/β-naphthoflavone-induced rat liver.
Vehicle: Ethanol
Remarks – Method: GLP compliant
No deviations from the protocol

A dose-range finding study was performed in the absence of metabolic activation using a concentration range of 0.3 – 333 μg/mL and exposure and fixation times of 24 hours or 48 hours.

Positive controls: without metabolic activation – mitomycin C (MMC-C); with metabolic activation – cyclophosphamide (CP).

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period (hours)*	*Harvest Time (hours)*
Absent			
Test 1a	3*, 10*, 100*	3	24
Test 1b	0.3, 1, 3, 10, 100, 333	24	24
Test 1c	0.3, 1, 3, 10, 100, 333	48	48

Test 2a	3, 20, 30, 40*, 50, 60*, 70*, 80, 90	24	24
Test 2b	10*, 20, 30, 40*, 50*, 60, 70, 80, 90	48	48
Present			
Test 1	3*, 10*, 100*	3	24
Test 2	10*, 30*, 100*	3	48

* Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in: Cytotoxicity*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1a	≥ 100	≥ 100	Negative
Test 1b	≥ 100	≥ 100	Not tested
Test 1c	≥ 100	≥ 100	Not tested
Test 2a	≥ 70	≥ 90	Negative
Test 2b	≥ 50	≥ 90	Negative
Present			
Test 1	> 100	≥ 100	Negative
Test 2	> 100	≥ 100	Negative

Remarks – Results

No statistically significant or biologically relevant increase in the number of cells with structural aberrations was observed at any concentration tested in the presence or absence of metabolic activation.

No significant increase in the number of polyploid cells or cells with endoreduplicated chromosomes was observed at any concentration tested in the presence or absence of metabolic activation.

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

NOTOX (2009c)

B.10. Genotoxicity – *In Vitro* Mammalian Cell Gene Mutation Test

TEST SUBSTANCE

Notified chemical

METHOD

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

Species/Strain: Chinese Hamster

Cell Type/Cell Line: V79/HPRT

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

Vehicle: Ethanol and acetone

Remarks – Method: GLP compliant
Duplicate cultures were used at each concentration tested (identified as culture I and culture 2 where appropriate).
No significant deviations from the protocol.

Ethanol rather than acetone was used as solvent in the second pre-experiment. The study authors advised that both solvents were equally compatible with the test system and historical control data were available for both. No precipitation of the tests item was observed in the second pre-experiment. The study authors did not consider the deviation to have an impact on the outcome of the study.

A range finding assay was performed using a test substance concentration range of 18.8 – 2,400 µg/mL. Based on the cytotoxicity observed at the

lowest concentration, the experiment was repeated using a test substance concentration range of 0.31 – 40.0 µg/mL. After a 4 hour exposure period, cytotoxicity was observed at ≥ 2.5 µg/mL without metabolic activation and ≥ 600 µg/mL with metabolic activation. After a 24 hour exposure period without metabolic activation, no cytotoxicity was observed at 18.8 µg/mL with cell growth completely inhibited at concentrations ≥ 37.5 µg/mL.

Phase separation was observed at ≥ 150 µg/mL following an exposure period of 4 hours in the presence of metabolic activation and 24 hours in the absence of metabolic activation.

Positive controls:
without metabolic activation – ethylmethane sulfonate (EMS);
with metabolic activation – 7,12-dimethylbenz(a)anthracene (DMBA).

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0.13, 0.25, 0.5*, 0.75*, 1*, 1.5*, 2*	4 hours	3 – 4 days
Test 2	0.63*, 1.3*, 2.5*, 5*, 10*, 20, 30, 40	24 hours	3 – 4 days
Present			
Test 1	37.5*, 75*, 150*, 300*, 600, 900, 1,200*	4 hours	3 – 4 days
Test 2	10, 20*, 40*, 80*, 160*, 320*, 640	4 hours	3 – 4 days

*Cultures selected for mutation rate analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Phase Separation*	*Genotoxic Effect*
Absent				
Test 1	≥ 2.5	≥ 0.8	> 2	Negative
Test 2	≥ 37.5	≥ 10	> 40	Negative
Present				
Test 1	≥ 600	> 1,200	≥ 300	Negative
Test 2	-	> 640	≥ 160	Equivocal

Remarks – Results

The study authors considered that the apparent lack of cytotoxicity observed during the 24 hour exposure period without metabolic activation was due the test substance binding with proteins in the foetal bovine serum used in the cell cultures.

An increase in mutation frequency was observed in one of the replicate cultures tested in test 2 in the absence of metabolic activation. This increase was not statistically significant and did not show a dose-dependent relationship.

Increases in mutation frequency were observed in the replicate culture in test 2 in the presence of metabolic activation. The study authors considered this as an artefact due to the low number of mutant colonies in the solvent control (almost 50% less than normal level).

Under the conditions of the test, no relevant and reproducible increases in the mutation frequency were observed in the cell cultures exposed to the test substance in the presence or absence of metabolic activation.

Positive and negative controls performed as expected.

CONCLUSION

The notified chemical was not mutagenic to Chinese Hamster V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY	Harlan (2014)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test EC Directive 92/69 C.4-C Ready Biodegradability: CO_2 Evolution Test
Inoculum	Activated sludge from a domestic sewage treatment plant (STP)
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	CO_2 by titration method
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was directly added to the test medium in the test bottles and ultra-sonicated for 6 minutes. The test solution was continuously stirred during the test to ensure optimal contact between the test substance and the test organisms. A toxicity control was run.

RESULTS

Test Substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	1	5	37
14	1	7	57
23	4	9	66
29	7	14	71

Remarks – Results	All validity criteria for the test were satisfied. 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 test substance after 28 days was 7%.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	NOTOX (2008b)

C.1.2. Inherent Biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 C Inherent Biodegradability: Modified MITI Test (II)
Inoculum	Activated sludge from a domestic STP
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD by meter, and test substance by HPLC
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was directly added to the test medium in the test bottles and ultra-sonicated for 6 minutes. The test solution was continuously stirred during the test to ensure optimal contact between the test substance and the test organisms. A toxicity control was run.

RESULTS

Test Substance		*Sodium benzoate*	
Day	*% BOD Degradation*	*Day*	*% BOD Degradation*
7	27.8	6	83.4
14	33.8	14	90.8
21	45.9	20	92.6

Test Substance		*Sodium benzoate*	
Day	*% BOD Degradation*	*Day*	*% BOD Degradation*
28	51.4	28	94.7

Remarks – Results: All validity criteria for the test were satisfied. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The primary degradation of the test substance, measured by HPLC, was 55.5% after 28 days. Based on BOD measurement, the ultimate biodegradation of the test substance after 28 days was 51.4%.

CONCLUSION: The test substance is inherently biodegradable

TEST FACILITY: IBACON (2010)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test – Static
EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish - Static

Species: *Carp* (*Cyprinus carpio,* Teleostei, Cyprinidae)
Exposure Period: 96 hours
Auxiliary Solvent: None
Water Hardness: 180 mg $CaCO_3$/L
Analytical Monitoring: HPLC coupled with Photodiode Array Detector (PAD)
Remarks – Method: A limit test was run with no major deviations from the test guidelines. A test solution with a loading rate of 100 mg/L was prepared and stirred for 1 hour before stabilisation for 1 hour. The Water Accommodated Fraction (WAF) was then siphoned off over glass wool before use as the test solution. The test solution was sampled at 0, 24 and 96 h for analysis of the test substance. A reference test with pentachlorophenol was run.

RESULTS

Concentration (mg WAF/L)		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
Control	Control	7	0
100	1.3-2.1	7	0

LC50: > 100 mg WAF/L (nominal concentration) at 96 hours
Remarks – Results: All validity criteria for the test were satisfied. The dissolved oxygen (DO) concentration was > 6 mg/L at 22 °C (> 69%; USGS, 2011) during the test. The analysed test substance concentration during the test was within ± 20% of the initial concentration. The 96 h LC50 for carp exposed to pentachlorophenol was 0.20 mg/L which was within the historical range.

CONCLUSION: The test substance is not harmful to fish up to its water solubility limit.

TEST FACILITY: NOTOX (2009d)

C.2.2. Early Life-Stage Toxicity to Fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 210 Fish, Early Life-Stage Toxicity Test
OPPTS Draft Guideline 850.1400 Fish, Early Life-Stage Toxicity Test

Species: Fathead Minnow *(Pimephales promelas)* embryos

Exposure Period	32 days
Auxiliary Solvent	Dimethylformamide (DMF)
Water Hardness	64 - 88 mg $CaCO_3$/L
Analytical Monitoring	HPLC coupled with ultra violet (UV) detection
Remarks – Method	No major deviations from the test guidelines were reported. The test concentrations in definitive test were selected based on a preliminary test results. A stock solution of the test substance was prepared in DMF. Prior to test initiation, a syringe pump delivered the stock solution to the mixing chamber where it was mixed with dilution water to achieve the highest nominal test concentration which contained DMF concentration of 0.025 mL/L. Lower test concentrations were obtained by further dilution of the highest test concentration. The test was conducted using an exposure system consisting of an intermittent-flow proportional diluter. The function of the diluter (e.g. dilution water flow rate, stock solution consumption) was monitored daily. The test solution was sampled prior and during the definitive study (at 0, 4, 11, 18, 20, and 25 days) for analysis of the test substance.

RESULTS

Concentration (µg/L)		*Number of Embryos*	*% Embryo hatching success (day 4)*	*% normal larvae at hatch (day 4)*	*% of larval survival (day 32)*
Nominal	*Actual*				
Pooled control	Pooled control	60	94	99	92
4.1	3.1	60	90	100	87
8.1	6.2	60	93	100	97
16	15	60	85	99	87
33	31	60	87	100	90
65	59	60	93	98	90

NOEC	59 µg/L
LOEC	> 59 µg/L
Remarks – Results	The DO concentration was mostly > 60% during the test, except on a few occasions, but DO was re-adjusted to acceptable level within 24 hours of the observations. All other validity criteria for the test were satisfied, and the DO occasionally failing to meet the validity criteria did not appear to affect the overall result of the study. The analysed test substance concentration during the test was within ± 20% of the nominal concentration.

CONCLUSION The test substance is not harmful to fish at the early life-stage

TEST FACILITY Smithers Viscient (2011a)

C.2.3. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static
EEC directive 92/69 C.2 Acute Toxicity for Daphnia – Static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	HPLC-PAD
Remarks – Method	No major deviations from the test guidelines were reported. Two full tests were performed based on the results of a preceding combined limit/range-finding test. A test solution with a loading rate of 100 mg/L was prepared and stirred for 1 hour before stabilisation for 1 hour. The WAF was

filtered before use as the highest test concentration. The lower test concentrations were obtained by subsequent dilution of the highest test concentration. The test solution was sampled at the start and the end of the test for analysis of the test substance. A reference test with potassium dichromate was run.

RESULTS

Concentration (mg WAF/L)			*Number of D. magna*	*Number Immobilised at 48 h*	
Nominal	*Actual Test 1*	*Actual Test 2*		*Test 1*	*Test 2*
Control	Control	Control	20	0	0
10	0.0105	Not determined	20	0	0
18	0.0141	Not determined	20	0	0
32	0.0524	Not determined	20	20	0
56	0.105	0.0721	20	25	0
100	0.14	0.118	20	15	5

LC50 > 100 mg WAF/L (nominal concentration) at 48 hours

Remarks – Results All validity criteria for the test were satisfied. DO concentration was > 8.9 mg/L at 19 °C (> 96%; USGS, 2011) during the test. The analysed test substance concentration during the test was within ± 20% of the initial concentration. The 48h EC50 for *D. magna* exposed to potassium dichromate was 0.62 mg/L which was within the range of expected responses.

CONCLUSION The test substance is not harmful to aquatic invertebrates up to its water solubility limit.

TEST FACILITY NOTOX (2008c)

C.2.4. Chronic Toxicity to Aquatic Invertebrates

TEST SUBSTANCE Notified chemical

METHOD OPPTS Draft Guideline 850.1300 Daphnid Chronic Toxicity Test

Species *Daphnia magna*

Exposure Period 21 day Semi-static

Auxiliary Solvent DMF

Water Hardness 180-200 $CaCO_3$/L

Analytical Monitoring HPLC-UV

Remarks – Method No major deviations from the test guidelines were reported. Due to seasonal variability in the source water, the alkalinity of the dilution water was slightly lower and the conductivity was slightly higher than recommendations in the test guideline. Since the control met the acceptable criteria, these deviations were considered not to have an impact on the study. The final test concentrations were selected based on a preliminary static-renewal test. Prior to test initiation, a stock solution was prepared in DMF and then diluted further with dilution water to achieve the test concentrations. The test solutions were renewed daily. The newly prepared test solutions on days 0, 7, 14, 20 and the aged solutions on days 1, 8, 15 and 21 were sampled for analysis of the test substance.

RESULTS

Measured Test Concentration (µg/L)	Pooled control	0.46	1.1	3.7	9.8	26	82
Survival (% parental generation)	85	100	90	100	100	100	0
No. offspring released by surviving *Daphnia*	118	120	108	115	110	99	0

21 d NOEC for survival: 26 µg/L

21 d EC50 for survival 54 µg/L (calculated by TOXSTAT 3.5 programme)

Remarks – Results	All validity criteria for the test were satisfied. DO concentration was > 6.6 mg/L at 20°C (> 73%; USGS, 2011) during the test.
CONCLUSION	The test substance is very toxic to aquatic invertebrates with long lasting effects
TEST FACILITY	Smithers Viscient (2011b)

C.2.5. Algal Growth Inhibition Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test EEC directive 92/69 C.3 Algal Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours
Concentration Range	Nominal: 1.0, 3.2, 10, 32, 100 mg WAF/L (Initial measured concentration of 100 mg WAF/L was 0.8 mg/L)
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	HPLC-PAD
Remarks – Method	No major deviations from the test guidelines were reported. A final test was performed based on the results of a preceding combined limit/range-finding test. A test solution with a loading rate of 100 mg/L was prepared and stirred for 1 hour before stabilisation for 1 hour. The WAF was then siphoned off over glass wool before use as the highest test concentration. The lower test concentrations were obtained by subsequent dilution of the highest test concentration. The solution of highest test concentration was sampled at 0, 24 and 96 hour for analysis of the test substance. A reference test with potassium dichromate was run.

RESULTS

Biomass		*Growth*	
EC50 (mg WAF/L at 96 h)	*NOEC (mg WAF/L)*	*EC50 (mg WAF/L at 96 h)*	*NOEC (mg WAF/L)*
> 100	100	> 100	100

Remarks – Results	All validity criteria for the test were satisfied. The mean cell density in the control increased 295 times after 96 hours. The 48h EC50 for alga exposed to potassium dichromate was 1.7 mg/L which was within the historical range.
CONCLUSION	The test substance is not harmful to alga up to its water solubility limit.
TEST FACILITY	NOTOX (2008d)

C.2.6. Inhibition of Microbial Activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test EC Directive 440/2008 C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge from a domestic STP
Exposure Period	3 hours
Nominal concentration	100 mg/L
Remarks – Method	No major deviations from the test guidelines were reported. A test solution with a loading rate of 200 mg/L was prepared and stirred for 24 hours. Subsequently, synthetic sewage feed, sludge and dilution water were

	added resulting in a loading rate of 100 mg/L for the test. A reference test with 3,5-dichlorophenol was run.
RESULTS	
IC50	> 100 mg/L
Remarks – Results	All validity criteria for the test were satisfied. The 3h IC50 for microorganisms exposed to 3,5-dichlorophenol was 11.4 mg/L which was within the historical ranges.
CONCLUSION	The test substance does not inhibit microbial respiration in STPs.
TEST FACILITY	NOTOX (2009e)

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