File No: LTD/1840

July 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Phenol, 3-propyl-

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.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1840	Firmenich Pty Limited	Phenol, 3-propyl-	Yes	≤ 1 tonne per annum	Fragrance ingredient

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*
Acute Toxicity (Category 4)	H302 – Harmful if swallowed H332 – Harmful if inhaled
Skin Corrosion (Category 1)	H314 – Causes severe skin burns and eye damage

In Australia, additional non-GHS hazard statements apply (see *Guidance on the Classification of Hazardous Chemicals Under the WHS Regulations* for further information; SWA, 2012a). Based on the available information, the following additional (non-GHS) hazard statement is also recommended:

AUH071 – Corrosive to the respiratory tract

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):

R20/22 Harmful by inhalation and if swallowed
R34 Causes burns

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

Hazard classification	*Hazard statement*
Acute aquatic toxicity (Category 2)	H401: Toxic to aquatic life

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

Based on the information available, when used at ≤ 0.1% in leave-on cosmetic products, ≤ 0.4% in air fresheners and rinse-off cosmetic products and ≤ 0.7% in other household products, 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:
  - Acute Toxicity (Category 4): H332 – Harmful if inhaled
  - AUH071 – Corrosive to the respiratory tract

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.

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

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(Material) Safety Data Sheet

- The (M)SDS of the notified chemical should reflect the above mentioned hazards.

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 processes, where possible
  - Ventilation system, including local exhaust ventilation

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

- 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:
  - Impervious gloves, eye protection, coveralls

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

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 0.1% in leave-on cosmetic products, ≤ 0.4% in air fresheners and rinse-off cosmetic products and ≤ 0.7% in other household products.

Disposal

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

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012b) or relevant State or Territory Code of Practice.

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the chemical is intended to be introduced at > 1% concentration;
- the concentration of the notified chemical exceeds or is intended to exceed 0.1% in leave-on cosmetic products, 0.4% in air fresheners and rinse-off cosmetic products and 0.7% in other household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- 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)SDS of the notified chemical provided by the notifier was 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)
Firmenich Pty Limited (ABN: 86 002 964 794)
73 Kenneth Road,
BALGOWLAH NSW 2093

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 claimed exempt from publication: other names, spectral data, degree of purity, impurities, additives/adjuvants and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

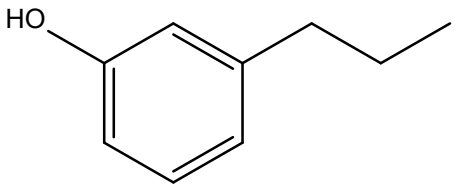
MARKETING NAME(S)
Phenol, 3-propyl-

CAS NUMBER
621-27-2

CHEMICAL NAME
Phenol, 3-propyl-

MOLECULAR FORMULA
$C_9H_{12}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
136.19

ANALYTICAL DATA
Reference HPLC-UV, NMR, FT-IR, GC-MS and UV/VIS spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 96%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid

Property	Value	Data Source/Justification
Freezing Point	< -20 °C	Measured
Boiling Point	232 °C at 97.9 kPa	Measured
Relative Density (D^{20}_4)	0.994 at 20 °C	Measured
Vapour Pressure	0.0028 kPa at 25 °C	Measured
Water Solubility	< 1 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Stable at pH 2-12	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.1 at 20 °C	Measured
Surface tension	50.1 mN/m (90% saturated solution)	Measured
Adsorption/Desorption	log K_{oc} = 2.25 at 35 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	111 °C at 97.2 kPa	Measured
Autoignition Temperature	505 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties.

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 not be manufactured in Australia. It will be imported into Australia as a component of compounded fragrance preparations and various formulated end-use cosmetic and household products (at a maximum concentration of 1%).

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
Sydney, by wharf or airport

IDENTITY OF RECIPIENTS
Firmenich Pty Limited.

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 1% concentration) will be imported as a component of fragrance formulations into Australia in lacquered drums typically of 180 kg size, but drums with sizes ranging from 5 kg to 100 kg may also be used. The products containing the notified chemical will be transported from the port of entry by road to the notifier's warehouse facilities for storage in its original packaging until distributed to the customer sites for reformulation.

The end-use consumer products containing the notified chemical at ≤ 0.7% concentration will be packaged in typical consumer-sized containers for retail sale.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products. The content in the final consumer products will vary, with the following proposed usage concentrations: leave-on cosmetic products (≤ 0.1%), air fresheners and rinse-off cosmetic products (≤ 0.4%) and other household products (≤ 0.7%).

OPERATION DESCRIPTION
No manufacturing, processing, reformulation or repackaging of the notified chemical will occur at the notifier's facility. The imported products containing the notified chemical will be stored at the notifier's facility until they are transported to customer facilities (in original importation packaging).

At the customer facilities, the procedures for incorporating the imported preparations containing the notified chemical into end-use products will likely vary depending on the type of product formulated, and may involve both automated and manual transfer steps. However, in general, the blending process will likely be highly automated and will occur in a fully enclosed environment. This will be followed by automatic filling of the finished products into containers of various sizes which will be distributed to retail outlets.

Household products
Household products containing the notified chemical at ≤ 0.7% concentration may be used by consumers and professional workers. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines or open processes, and manually applied by rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 0.4% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator

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 workers	Unspecified	Unspecified
Mixer	4	2
Drum handling	4	2
Drum cleaning	4	2
Maintenance	4	2
Quality control	0.5	1
Packaging	4	2
End users (professionals)	Unspecified	Unspecified

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemical as a component of the imported fragrance preparations at ≤ 1% concentration or end-use products at ≤ 0.7% concentration, only in the event of accidental rupture of containers.

At the notifier facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing the notified chemical at ≤ 1% concentration. Exposures of these workers will be limited to situations where packaging is accidentally breached. If such an event occurs, workers may be exposed through dermal, ocular or perhaps inhalation exposure.

Formulation of end products

During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at ≤ 1% concentration may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection and suitable gloves.

Beauty care and cleaning professionals

Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤ 0.4% concentration) to clients (e.g. hair dressers, workers in beauty salons) or the use of household products (at ≤ 0.7% concentration) in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or less extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of the cosmetic and household products at ≤ 0.7% concentration. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

A combined internal dose of 0.3366 mg/kg bw/day was estimated using data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used (SCCS, 2012; Cadby *et al.*, 2002; Loretz *et. al.*, 2006; ACI, 2010; specific use details of the notified chemical are considered as exempt information). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic and household products that may contain the notified chemical.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 between 300 - 2000 mg/kg bw; harmful
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 between 1.08 - 4.98 mg/L/4 hour; harmful
Rabbit, skin irritation	corrosive
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NO(A)EL 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	equivocal
Genotoxicity – in vitro mammalian cell micronucleus test	non genotoxic

Toxicokinetics, metabolism and distribution.
Based on the water solubility (< 1 g/L at 20 °C), partition coefficient (log P_{ow} = 2.1 at 20 °C) and the low molecular weight (136.19) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are possible. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
Acute toxicity studies in rats showed that the notified chemical is harmful via the oral and inhalation routes. While the notified chemical was found to be of low toxicity via the dermal route, it is noted that a single animal was found dead 5 days after dosing and that corrosive effects were noted at the site of test substance application.

Irritation and sensitisation.
The notified chemical was corrosive to the skin of a single rabbit after four hours of exposure. Based on the results of the skin irritation test, no ocular irritation study was conducted due to the likely adverse effects on the eyes.

The notified chemical was not a sensitiser in a local lymph node assay (LLNA), under the conditions of the test.

Repeated dose toxicity.
In a 28 day repeat dose study by oral gavage, rats were administered the notified chemical at 20, 50 and 150 mg/kg bw/day. A NO(A)EL of 150 mg/kg bw/day was established, based on the absence of treatment-related, toxicologically-significant effects at all doses tested.

Mutagenicity/Genotoxicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study.

Equivocal results were obtained in an *in vitro* mammalian chromosome aberration study, with statistically significant increases in the number of cells with chromosome aberrations noted at cytotoxic concentrations of the test substance, in the presence of metabolic activation. An expert opinion (P. Jenkinson) was provided, which discussed the results of this study and indicated that there were several characteristics of the positive response that were typical of toxicity-induced false positive response (e.g. related to the shape of the toxicity dose-response curve and concentration required to replicate the response). A subsequent *in vitro* micronucleus study, in the presence of metabolic activation, showed no significant increase in the frequency of cells with micronuclei.

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***
Acute Toxicity (Category 4)	H302 – Harmful if swallowed H332 – Harmful if inhaled
Skin Corrosion (Category 1)	H314 – Causes severe skin burns and eye damage

In Australia, additional non-GHS hazard statements apply (see *Guidance on the Classification of Hazardous Chemicals Under the WHS Regulations* for further information; SWA, 2012a). Based on the available information, the following additional (non-GHS) hazard statement is also recommended:

AUH071 – Corrosive to the respiratory tract

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):

R20/22	Harmful by inhalation and if swallowed
R34	Causes burns

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation
Exposure of workers to the notified chemical (at ≤ 1% concentration) may occur during blending operations. While the notified chemical is considered to be harmful via the oral route, ingestion is unlikely under the occupational settings described. The notified chemical has the potential to cause skin burns and eye damage and is harmful if inhaled. Therefore, although the chemical will only be used at ≤ 1% concentration, caution should be exercised when handling the notified chemical during reformulation processes.

Therefore, provided that control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical at up to ≤ 0.7% concentration, similar to public use. Therefore, 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.

6.3.2. Public Health
Members of the public may experience repeated exposure to the notified chemical through the use of the cosmetic and household products (≤ 0.7% concentration in individual products).

Acute toxicity and irritation
The notified chemical is considered to be harmful via the oral and inhalation routes and has the potential to cause skin burns and eye damage. However, these effects are not expected from use of the notified chemical at the proposed concentrations in cosmetic and household products.

Repeated dose toxicity
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.3366 mg/kg bw/day (see Section 6.1.2) and the NO(A)EL of 150 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on the notified chemical. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. Using the above mentioned NO(A)EL, a MoE of 446 was estimated, which is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.1% in leave-on cosmetic products, ≤ 0.4% in air fresheners and rinse-off cosmetic products and ≤ 0.7% in other household products.

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 into Australia as a fragrance component of compounded formulations and various formulated end-use cosmetic and household products. Environmental release of the notified chemical during transportation and storage is expected to be minimal and will be limited to accidental spills or leaks of drums.

It is expected that the reformulation processes will involve blending operations that will be highly automated. It is expected to occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes. A total of 0.2% of waste is expected to be generated from blending or formulation activities as a result of spills and residues.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to enter the aquatic compartment during use of the various end-use products into which it will be incorporated. Cosmetic products will be washed off the hair and skin and will be released to sewers. Cleaning products will also be diluted in water and will be released to sewers. It is estimated that a maximum of 3% of the consumer products will remain in the consumer containers once the consumer product is used up. These containers are expected to be sent to landfill or to be recycled.

RELEASE OF CHEMICAL FROM DISPOSAL
Containers containing residual notified chemical are expected to be sent to landfill or to be recycled.

7.1.2. Environmental Fate
The notified chemical is readily biodegradable based on the provided study report. For the details of the environmental fate study please refer to Appendices C. The notified chemical has a low log P_{OW} of 2.1, and therefore, the bioaccumulative potential in aquatic organisms is not considered to be a concern.

The vapour pressure of the notified chemical of 0.0028 kPa at 25 °C indicates a high volatility. Based on a calculated (AOPWIN v 1.92; US EPA, 2011) half-life of 1.5 hours through atmosphere oxidation, it is not considered to be persistent in the air.

Most of the notified chemical is expected to be released into sewer systems after use of the associated products. A small amount of the notified chemical may be released to landfill as container residues or spills or thermally decomposed during containers' recycling, forming water and oxides of carbon. In landfill, the notified chemical is not expected to leach given the medium adsorption/desorption constant. In sewage treatment plants (STPs), a small proportion of the notified chemical may be removed by adsorption to sludge sediment given the low log K_{OC} of 2.25, and be disposed of to landfill or fields. The majority of the notified chemical is expected to be released into public waters. In water or soil/landfill, the notified chemical is expected to undergo biotic or abiotic degradation processes, forming water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)
The predicted environmental concentration (PEC) has been calculated assuming 100% release of the notified chemical into sewer systems nationwide. Based on the SimpleTreat model (EC, 2003), 92% of the notified chemical is expected to be removed from water surface by evaporation (75%) and sludge adsorption (17%).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	92%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.05	µg/L
PEC - Ocean:	0.005	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of ~ 0.05 µg/L may potentially result in a soil concentration of approximately 0.3 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 1.6 µg/kg and 3 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 10.8 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 5.7 mg/L	Toxic to Aquatic invertebrates
Algal Toxicity	72 h EC50 = 18 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h EC50 = 110 mg/L	Not toxic to bacterial respiration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is considered to be toxic to aquatic invertebrates and harmful to fish and algae and is formally classified as 'Acute Category 2: Toxic to aquatic life'. On the basis of its ready biodegradability, the notified chemical has not been classified for its chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated and presented in the table below. An assessment factor of 100 has been used to derive the PNEC as ecotoxicity data for aquatic species as three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
EC50 (Daphnia)	5.7 mg/L
Assessment Factor	100
PNEC:	57 µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.05	57	0.0008
Q - Ocean	0.005	57	0.00008

The Risk Quotients (Q = PEC/PNEC) have been calculated to be < < 1 for both river and ocean compartments. The notified chemical is not expected to persist in the environment as it is readily biodegradable, and is not expected to bioaccumulate. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import volume and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -20 ± 0.5 °C

Method OECD TG 102 Melting Point/Melting Range.
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks The test material remained unchanged in appearance during cooling. The freezing temperature was determined to be < 253 ± 0.5 K (-20 ± 0.5 °C)
Test Facility Firmenich (2013)

Boiling Point 232 ± 2 °C at 97.9 kPa

Method OECD TG 103 Boiling Point.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Siwoloboff method.
Test Facility Firmenich (2013)

Relative Density 0.994 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Oscillating density meter method was used. The apparatus was calibrated using toluene and trichloroethylene as reference standards.
Test Facility Firmenich (2013)

Vapour Pressure 0.0016 kPa at 20 °C
0.0028 kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks Isothermal thermogravimetric effusion method.
Test Facility WIL Research Europe B.V (2013a)

Water Solubility < 1 g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method
The concentration of test substance in the sample solutions was determined by high performance liquid chromatography (HPLC).
Test Facility Firmenich (2013)

Hydrolysis as a Function of pH Stable at pH 2-12

Method OECD TG 111 Hydrolysis as a Function of pH.

The notified chemical was added in the pH buffers (at pH 2, 5, 7, 8.5 and 12) to reach concentrations in the range of 200 - 300 ppm. The mixtures were then kept in an oven at 40 °C. Small aliquots of the test solutions were extracted using an organic solvent containing a hydrocarbon standard on a regular basis throughout the test. The extracts were analysed by gas chromatography.

pH	*T (°C)*	*t½ (days)*
2	40	> 365
5	40	> 365
7	40	> 365
8.5	40	> 365
12	40	> 365

Remarks The determined half-life at different pH indicates that the notified chemical is stable

between pH 2-12.
Test Facility Firmenich (2014)

Partition Coefficient (n-octanol/water) log Pow = 2.1at 20 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method
Test Facility Firmenich (2013)

Surface Tension 50.1 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% saturated aqueous solution. The notified chemical is considered to be surface active.
Test Facility WIL Research Europe B.V (2013b)

Adsorption/Desorption log K_{oc} = 2.25 at 35 °C

Method OECD TG 121 Estimation of the Adsorption Coefficient (K_{oc}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks The principle of the test method is similar to that of the OECD guideline no. 117.
Test Facility WIL Research Europe B.V (2013c)

Flash Point 111 ± 2 °C at 97.2 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks Closed cup equilibrium method.
Test Facility Firmenich (2013a)

Autoignition Temperature 505 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility WIL Research Europe B.V (2013a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity - Fixed Dose Method. EC Council Regulation No 440/2008 B.1 Acute Toxicity (Oral).
Species/Strain	Rat/RccHan™:WIST
Vehicle	Arachis oil BP (300 mg/kg bw) or none (2000 mg/kg bw)
Remarks - Method	No significant protocol deviations. GLP compliance.

RESULTS

Sighting Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	300	0/1
2	1 F	2000	1/1*

*Killed for humane reasons one hour after dosing

Signs of Toxicity	The animal treated with 2000 mg/kg bw exhibited increased salivation and prostration and was killed for humane reasons one hour after dosing. The animal treated with 300 mg/kg bw showed no signs of systemic toxicity.
Effects in Organs	The animal treated at 2000 mg/kg bw showed mottled appearance of the liver, dark kidneys, reddened oesophagus, raised limiting ridge and off white opaque fluid in the stomach, thickened gastric mucosa with an off white substance adhering to the lining of the glandular region, thickened and reddened non-glandular epithelium of the stomach and red coloured fluid filled bladder. No abnormalities were noted in the animal treated with 300 mg/kg bw.

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	4 F	300	0/4

LD50	Between 300 - 2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were observed.
Effects in Organs	No abnormalities were noted.
Remarks - Results	Weight gains were observed in all animals treated at 300 mg/kg bw.

CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	Harlan Laboratories Ltd (2012a)

B.2. Acute toxicity – dermal

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/RccHan™:WIST
Vehicle	None
Type of dressing	Semi-occlusive.
Remarks - Method	The contact period of the bandage was approximately 25 hours instead of 24 hours. GLP Compliance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	1 F/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Adverse skin reactions prevented evaluation of erythema and oedema in all animals throughout the study. Effects noted included light brown discolouration of the epidermis, loss of skin elasticity and flexibility, scabbing, scab lifting to reveal bleeding, dried blood, further deep scabbing or glossy skin, scab undulating, haemorrhage of dermal capillaries and well-defined erythema surrounding other skin reactions. Reactions were noted up to and including day 14.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed. One female animal was found dead 5 days after dosing.
Effects in Organs	Abnormalities noted in the dead female rat were dark liver, dark kidneys and epithelial sloughing of the gastric mucosa and non-glandular epithelium of the stomach. No abnormalities were noted in the remaining animals.
Remarks - Results	Five animals (2/5 M and 3/4 F) showed bodyweight loss during the first week but showed weight gains during the second week. The remaining surviving animals showed expected weight gains throughout the study.

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY Harlan Laboratories Ltd (2012b)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 436 Acute Inhalation Toxicity – Acute Toxic Method.

Species/Strain	Rat/RccHan^{TM}:WIST
Vehicle	None
Method of Exposure	Nasal exposure only.
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size*	Group 1 - 2.97 µm (65% < 4 µm) Group 2 - 2.08 µm (81.4% < 4 µm)
Remarks - Method	GLP Compliance. For Group 2 animals, the observation period was extended to 35 days.

*Mean Mass Aerodynamic Diameter (µm)

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	3 per sex	16.5	4.98	4/6 (2/3 M and 2/3 F)
2	3 per sex	3.82	1.08	2/6 (1/3 M and 1/3 F)

LC50	Between 1.08 – 4.98 mg/L/ 4 hours
Signs of Toxicity	For group 1 animals, 2 animals (1 M and 1 F) were found dead during the exposure period (at ~ 3 hours). An additional female animal was found dead the day following exposure and an additional male was humanely killed 5 days following exposure. Decreased respiratory rate (during and/or after exposure) and wet fur (during exposure) were observed in all animals. On removal, the surviving animals also exhibited noisy/laboured and/or gasping respiration, ataxia, hunched posture, pilo-erection and red/brown staining around the eyes and snout. In the male killed on day 5 following exposure, emaciation, dehydration and hypothermia were also noted prior to death. The two surviving animals recovered by day 12 and

	day 13. For group 2 animals, 1 male and 1 female were humanely killed on days 14 and 29, respectively. The animals showed signs of toxicity similar to that of the group 1 animals. Sneezing was observed in all animals. Recovery from exposure was observed in three out of the four animals that survived on day 26, with the remaining animal that survived recovering by day 35.
Effects in Organs	Animals that died or that were killed before the end of the study period exhibited the following: Lungs – haemorrhagic or abnormally dark (Group 1 animals), pale with dark patches (Group 2 animals); Liver – dark (Group 1 animals); Stomach – gaseous distension (Group 1 animals); Small Intestine – gaseous distension (Group 1 and 2 animals); Large intestine – gaseous distention (Group 1 and 2 animals). No macroscopic abnormalities were detected in 2 surviving animals from Group 1 and 2/4 surviving Group 2 animals. Pale lungs and dark patches on the lungs were seen in one surviving animal from group 2. This animal (and another surviving animal) also showed gaseous distension of the small and large intestine.
Remarks - Results	Weight loss was observed in animals of both groups from day 0 to day 3. The 2 surviving animals in group 1, showed weight gains at the subsequent observations. Two males and one female animal in group 2 showed further body weight losses between days 3 to 7. Weight losses were also noted in this female between days 28-35 and in the animals humanely killed, prior to their deaths. The study authors noted that the delay in recovery for the group 2 animals could be attributed to the smaller particle size achieved during exposure (relative to Group 1), which may have resulted in animals struggling to clear their lungs after the exposure period. The study authors also noted that the deaths during the study may have been mainly attributable to local toxicity.
CONCLUSION	The notified chemical is harmful via inhalation.
TEST FACILITY	Harlan Laboratories Ltd (2012c)

B.4. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White, (SPF)
Number of Animals	1 M
Vehicle	None
Observation Period	1 hour
Type of Dressing	Semi-occlusive.
Remarks - Method	The study was performed on a single rabbit (4-hour exposure). Due to the nature of the response observed (see below), the rabbit was sacrificed and no further animals tested.
RESULTS	
Remarks - Results	Severe erythema and grey discolouration of the treated skin area was noted 1 hour after exposure. The animal was subsequently sacrificed. At sacrifice, many scabs were also observed on the treated skin area.

CONCLUSION The notified chemical is corrosive to the skin.

TEST FACILITY WIL Research Europe B.V (2014a)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	Acetone/ Olive oil (4:1)
Positive Control	α-Hexylcinnamaldehyde tech., 85%
Remarks - Method	No significant protocol deviations GLP Compliance.

A preliminary screening test was performed using four mice (1/dose) at concentrations 50%, 25%, 10% or 5%. Animals treated with 50% and 25% showed signs of systemic toxicity and were humanely killed on day 1 and 2, respectively. Therefore, 10% of the notified chemical was chosen as the highest dose for the main test (no signs of systemic toxicity or excessive local irritation were noted in the animal treated at this dose).

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/animal)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	3236.52	-
2.5	6472.77	2.0
5	6625.33	2.05
10	7544.96	2.33
Positive Control		
25%	14511.24	4.48

Remarks - Results No signs of systemic toxicity were noted in the test or control animals.
The positive control elicited a stimulation index > 3, confirming the validity of the test system.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical, under the conditions of the study.

TEST FACILITY Harlan Laboratories Ltd (2014a)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Council Regulation No 440/2008 B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain	Rat: Crl:WI(Han) (outbred, SPF-Quality)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Propylene glycol
Remarks - Method	GLP Compliance. The dose selection was based on the results of a 5 day range finding study,

in which 3 females/dose were treated with 150, 500 and 1000 mg/kg bw/day of the notified chemical. No mortalities occurred at 150 mg/kg bw/day. Mortalities, severe clinical signs and corrosive effects in the forestomach were reported in animals treated with 1000 mg/kg bw/day and 500 mg/kg bw/day.

Histopathologic examination was only performed on control and high dose animals.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	20	0/10
mid dose	5 per sex	50	0/10
high dose	5 per sex	150	0/10

Mortality and Time to Death
No unscheduled deaths were reported during the study.

Clinical Observations
Salivation was observed after dosing in the majority of the animals treated at the highest dose (150 mg/kg bw/day). The study authors considered this observation to be a physiological response and possibly related to the irritancy/taste of the test substance. Rales observed in three males and three females treated with the highest dose were considered by the study authors to be incidental and of no toxicological significance.

Hearing ability, pupillary reflex, static righting reflex and grip strength were reported to be normal in all treated animals. Bodyweight gain was in the same range as controls. Food consumption was also reported to be similar to that of the control group.

Laboratory Findings – Clinical Chemistry, Haematology
No treatment related haematological or clinical chemistry changes were observed in animals, with any statistically significant changes occurring without a dose-response relationship, or considered by the study authors to be within the normal range for the strain and age of rats.

Effects in Organs
No toxicological significant macroscopic findings were noted at necropsy. (incidental findings were considered by the study authors to be within the range encountered among the strain and age of rat).

Statistically significant decreases in prostate weight in males treated at 50 mg/kg bw/day (absolute) and 150 mg/kg bw/day (absolute and relative) were considered by the study authors to be of no toxicological significance due to the lack of correlating histopathological findings.

There were no microscopic findings considered by the study authors to be treatment related (findings occurred in at comparable levels to controls and/or were considered to be within the range encountered among the strain and age of rat).

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 150 mg/kg bw/day in this study, based on the absence of treatment-related toxicologically-significant effects at all tested doses.

TEST FACILITY WIL Research Europe B.V (2014b)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified 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 and Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5 - 5000 µg/plate b) Without metabolic activation: 5 - 5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. GLP Compliance.

A preliminary toxicity test was conducted using strains TA100 and WP2uvrA and ten concentrations of the test substance (0.15-1500 µg/plate, with and without metabolic activation, plate incorporation method).

Five positive controls were used in parallel with the test substance. N-ethyl-N'-nitro-N-nitrosoguanidine, 9-Aminoacridine and 4-Nitroquinoline-1-oxide were used in the absence of S9-mix. 2-Aminoanthracene and Benzo(a)pyrene were used with S9-mix.

Test 1 was conducted using the plate incorporation method and Test 2 was conducted using the pre incubation method.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥1500	≥ 1500	> 5,000	Negative
Test 2		≥ 500	> 5,000	Negative
Present				
Test 1	≥ 1500	≥ 1500	> 5,000	Negative
Test 2		≥ 1500	> 5,000	Negative

Remarks - Results

Reduction in the growth of the bacterial background lawn was visible in all strains from 1500 µg/plate with and without metabolic activation (or 500 µg/plate in Test 2 for strains TA100, TA1535 and TA1537 in the absence of metabolic activation).

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

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

CONCLUSION

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

TEST FACILITY

Harlan Laboratories (2012d)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2008/440/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes/peripheral
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. GLP Compliance

A preliminary dose range finding study with 3 hour exposure time (with S9-mix), or 3 hour, 24 hour and a 48 hour exposure time (without S9-mix) was conducted. Precipitation was observed in the culture medium from 1000 µg/mL.

Vehicle and positive controls (mitomycin C without metabolic activation and cyclophosphamide with metabolic activation) were used in parallel with the test material.

It is noted that only 200 cells were scored/dose. The current (2014) version of this guideline indicates that at least 300 cells should be scored (increases the statistical power of the test).

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 1*, 10, 30*, 60, 100*, 150	3 hours	24 hours
Test 2	0*, 1*, 3, 10, 30*, 70, 100, 150*	24 hours	24 hours
	0*, 1*, 3*,5, 10, 30*, 70, 100, 150	48 hours	48 hours
Present			
Test 1	0*, 1*, 10, 30*, 60*, 100, 150	3 hours	24 hours
Test 2	0*, 1*, 10, 30, 50, 100*, 150*	3 hours	48 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 100	≥ 100	>150	Negative
Test 2	≥ 100	≥ 100	>150	Negative
	≥ 10	>10	>50	Negative
Present				
Test 1	≥ 100	≥ 60	>150	Equivocal
Test 2		≥ 150	>150	Equivocal

Remarks - Results

In Tests 1 and 2, mitotic inhibition was observed at all dose levels of both exposure groups. However, it is noted that a relatively flat response curve was observed such that the higher doses all showed similar levels of toxicity in each group.

In test 1, no statistically significant or biologically relevant increase in the number of cells with chromosome aberrations was observed in the absence of S9-mix. In the presence of S9-mix, a statistically significant increase in the number of cells with chromosome aberrations was observed at the highest, cytotoxic (53% mitotic inhibition) concentration only. Aberrations were predominantly chromatid breaks and no exchange aberrations were observed.

In test 2, no statistically significant or biologically relevant increase in the number of cells with chromosome aberrations was observed in the absence

of S9-mix. In the presence of S9-mix, a statistically significant increase in the number of cells with chromosome aberrations at the highest cytotoxic, concentration was observed. The aberration types were predominantly chromatid breaks (a single exchange aberration was observed).

The study authors questioned the biological significance of the results and noted the 'hockey-stick' type dose-response curve (2.5-fold higher concentration required to elicit a response in Test 2 than Test 1). The study authors also noted that both in the absence and presence of S9-mix, the test substance did not increase the number of polyploid cells or the number of cells with endoreduplicated chromosomes.

CONCLUSION The results for the notified chemical were equivocal for clastogenicity to human lymphocytes treated in vitro, under the conditions of the test.

TEST FACILITY WIL Research Europe B.V (2014c)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 487 In vitro Mammalian Cell Micronucleus Test.

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes/peripheral
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks - Method	GLP Compliance.

No exposures in the absence of metabolic activation were performed.

A preliminary toxicity study was performed with S9-mix (4 hour exposure, followed by 28 hour incubation in treatment-free media). The dose range was 7.5, 15, 30, 60, 90, 120, 180, 240 and 300 µg/mL. No precipitate was observed at the end of the exposure period (parallel blood free cultures; the media was darker at 240 and 300 µg/mL) and the blood pellets were darker in colour in all the dose levels. Haemolysis was observed at ≥ 120 µg/mL. Binucleate cells were present at up to 240 µg/mL.

Vehicle and positive controls (cyclophosphamide) were used in parallel with the test material.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Recovery Period*
Present			
Test 1	0*, 3.75*, 7.5*, 15*, 30*, 45, 50, 60, 90, 120 and 160	4 h	28 h

*Cultures selected for micronucleus analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1	≥ 90	≥ 30	> 160	Negative

Remarks - Results The notified chemical in the presence of metabolic activation did not induce a statistically significant increase in the frequency of cells with micronuclei.
The positive and vehicle control values confirmed the validity of the test

	system.
CONCLUSION	The notified chemical was not genotoxic to human lymphocyte cells treated in vitro under the conditions of the test.
TEST FACILITY	Harlan Laboratories (2014b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD)
Remarks - Method	No significant protocol deviations. GLP Compliance

An amount of test substance (500 mg) was dissolved in mineral medium with the aid of ultrasonication for approximately 15 minutes and the volume adjusted to 500 mL to give a 1000 mg/L stock solution. An aliquot (50 mL) of this stock solution was diluted with mineral medium (445 mL) and inoculum (5 mL) to give the final test concentration of 100 mg/L. The volumetric flasks containing the stock solution and the test concentration were inverted several times to ensure homogeneity.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	58.5	7	17
14	66.5	14	70
21	79	21	74
28	85.5	28	75

Remarks - Results

All the test validity criteria were met.

The toxicity control attained 52% degradation after 14 days and 82% degradation after 28 days. Therefore the notified chemical was not toxic to the sewage treatment micro-organisms used in the study.

The test substance attained 86% degradation after 28 days and satisfied the 10-Day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation rate exceeding 10%. The test substance can therefore be considered to be readily biodegradable under the strict terms and conditions of OECD Guideline No. 301F.

CONCLUSION The notified chemical is readily biodegradable.

TEST FACILITY Harlan Laboratories Ltd (2012e)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test Semi-Static test
Species	Zebra fish (*Danio rerio*)
Exposure Period	96 hour
Auxiliary Solvent	None
Water Hardness	135 mg $CaCO_3$/L

Analytical Monitoring	HPLC
Remarks – Method	No significant protocol deviations. GLP Compliance

0.400g test substance was mixed with test water followed ultrasonication for 10min. This mixture was transferred into 5 L-jar and diluted with test water to 4000 mL to obtain the nominal concentration of 100 mg/L test suspension. This suspension was stirred with a magnetic stirrer for about 2 hours to get a clear solution with a nominal concentration of 100 mg/L test stock solution. A series of dilutions was made from this saturated solution to give the required test concentrations of 3.48, 5.21, 7.82, 11.7 and 17.7% nominal solutions.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*			
Nominal		*24 h*	*48 h*	*72 h*	*96 h*
Control	10	0	0	0	0
3.48	10	0	0	0	0
5.21	10	0	0	0	0
7.82	10	0	0	0	0
11.7	10	2	3	5	7
17.6	10	10	10	10	10

LC50	10.8 mg/L at 96 hours.
NOEC	7.85 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied.

The measured concentrations of test solutions were maintained within ±20% of the nominal concentration of the test substance during the renewal period of 24 h. Therefore, the test results are based on nominal concentrations.

CONCLUSION The notified chemical is harmful to fish

TEST FACILITY GCDM (2014)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test - Static. EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia -
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	Ultra Performance Liquid Chromatography (UPLC)
Remarks - Method	No significant protocol deviations. GLP Compliance

The test substance (100 mg) was dissolved in 1 L of test water. The mixture was stirred magnetically for 15 minutes to give a clear and colourless stock solution. The lower test concentrations were prepared by subsequent dilutions in test medium.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control		20	0	0
1.0		20	0	0
1.8		20	0	0
3.2		20	0	0
5.6		20	0	8
10		20	16	20

LC50	5.7 mg/L at 48 hours
NOEC (or LOEC)	3.2 mg/L at 48 hours
Remarks - Results	The measured concentrations of test solutions were maintained within ±20% of the nominal concentration of the test substance during the renewal period of 24h. Therefore, the test results are based on nominal concentrations.
CONCLUSION	The notified chemical is toxic to aquatic invertebrates
TEST FACILITY	WIL Research Europe B.V (2013d)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Council Regulation No 440/2008 C.3 Algal Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0.32, 1.0, 3.2, 10, 32 and 100 mg/l.
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	
Remarks - Method	All validity criteria for the test were satisfied. No significant protocol deviations. GLP Compliance The test substance (100 mg) was dissolved in 1 L of test water. The mixture was stirred magnetically for 15 minutes to give a clear and colourless stock solution. The lower test concentrations were prepared by subsequent dilutions in test medium.

RESULTS

Biomass		*Growth*	
EyC50	*NOEC*	*ErC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L*	*mg/L*
6	0.32	18	1

Remarks - Results	All validity criteria for the test were satisfied. The measured concentrations of test solutions were maintained within ±20% of the nominal concentration of the test substance during the renewal period of 24 h. Therefore, the test results are based on nominal concentrations.
CONCLUSION	The notified chemical is harmful to algae
TEST FACILITY	WIL Research Europe B.V (2013e)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 3.2, 10, 32, 100 and 320 mg/l.
Remarks – Method	No significant protocol deviations. GLP Compliance
RESULTS	
EC50	110 mg/L
NOEC	> 110 mg/L
Remarks – Results	All validity criteria for the test were satisfied
CONCLUSION	The notified chemical is not inhibitory to microorganism's respiration.
TEST FACILITY	WIL Research Europe B.V (2013f)

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