File No: LTD/1895

April 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Ethanone, 1-(5-propyl-1,3-benzodioxol-2-yl)-

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.

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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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/1895	Firmenich Pty Limited	Ethanone, 1-(5-propyl-1,3-benzodioxol-2-yl)-	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*
Skin Irritation (Category 2)	H315 – Causes skin irritation

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):
R38: Irritating to Skin

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

Hazard classification	*Hazard statement*
Acute Category 3	H402 – Harmful to aquatic life
Chronic Category 3	H412 – Harmful to aquatic life with long lasting effects

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.

Based on the available information, when used as a fragrance component in a variety of cosmetic and household products at ≤ 1%, 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:
  - H315 – Causes skin irritation

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.

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

Disposal

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

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by 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 concentration of the notified chemical exceeds or is intended to exceed 1% in cosmetic and household products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical as 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;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

(Material) Safety Data Sheet
The (M)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 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, analytical data, degree of purity, impurities and additives/adjuvants.

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

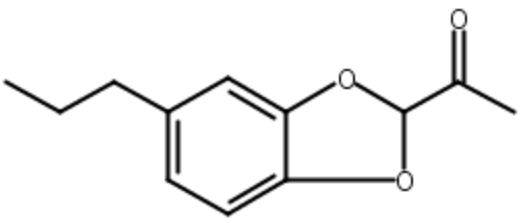
MARKETING NAME(S)
Ethanone, 1-(5-propyl-1,3-benzodioxol-2-yl)-

CAS NUMBER
1370699-98-1

CHEMICAL NAME
Ethanone, 1-(5-propyl-1,3-benzodioxol-2-yl)-

MOLECULAR FORMULA
$C_{12}H_{14}O_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
206.24 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	Not determined	Decomposes at 240 °C prior to boiling
Density	1,101 kg/m^3 at 20 °C	Measured
Vapour Pressure	5.9 × 10^{-4} kPa at 25 °C	Measured
Water Solubility	2.16 g/L at pH 4.1 at 20 °C	Measured
Hydrolysis as a Function of pH	Stable at pH ≤ 7 Unstable at pH > 7	Measured (in-house method)*
Partition Coefficient (n-octanol/water)	log Pow = 2.69	Measured
Surface tension	39.46 mN/m at 20 °C (1 g/L aqueous solution)	Measured
Adsorption/Desorption	log K_{oc} = 2.0-2.3 at 23.6 °C (soil) log K_{oc} = 2.0-2.5 at 23.6 °C (sewage sludge)	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	135 °C at 101.3 kPa	Measured
Autoignition Temperature	370 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply 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 be imported into Australia in its pure form or as a component in a fragrance formula (at a concentration ≤ 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

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in either its pure form or as a component of fragrance preparations containing the notified chemical (at ≤ 1% concentration). The notified chemical will be imported and distributed in tightly closed lacquered drums of 180, 100, 50, 25, 10 or 5 kg in size. They will be transported by road to the Firmenich Ltd warehouse for storage and then distributed to reformulation sites. It is also possible that the notified chemical will be transported directly to the customer's facilities from the port of entry. End-use products will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products at ≤ 1%.

OPERATION DESCRIPTION
The procedures for incorporating the imported preparations (in pure form or at ≤ 1% concentration) into end-use products will likely vary depending on the nature of the cosmetic and personal care/household cleaning products formulated, and may involve both automated and manual transfer steps. It is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed/contained environment, followed by automated filling (using sealed delivery systems) of the reformulated end-use products into containers of various sizes.

The end-use products containing the notified chemical (at ≤ 1% concentration) may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

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	Unknown	Unknown
Mixer	4	2
Drum handling	4	2
Drum cleaning	4	2
Maintenance	4	2
Quality Control	0.5	1
Packaging	4	2
Salon Workers	Unspecified	Unspecified
Cleaners	Unspecified	Unspecified

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical, in its pure form or as a component of the imported preparations (at a concentration of ≤ 1%), only in the event of accidental rupture of containers.

Formulation of end use products
During reformulation, dermal, ocular and potentially inhalation exposure of workers to the notified chemical (in pure form) may occur during weighing and transfer stages, equipment preparation, blending, quality control analysis and cleaning and maintenance of equipment, Exposure is expected to be minimised through the use of mechanical exhaust ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as gloves, respirator, eye protection and protective clothing.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at ≤ 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hairdressers, workers in beauty salons) or in the cleaning industry. Such professionals may use 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 lesser 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 (at a concentration ≤ 1%) through the use of the household cleaning products, perfumes and both rinse-off and leave-on cosmetic and personal care products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible particularly if products are applied by spray.

Data on typical use patterns of cosmetic product categories in which the notified chemical may be used are shown in the following table (SCSS, 2012; Cadby *et al*., 2002). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. An adult bodyweight of 64 kg was used for calculation purposes. Based on absence of dermal absorption data on the notified chemical, a dermal absorption of 100% was assumed for the notified chemical.

- Cosmetic products (Dermal exposure)

Product type	**Amount** (mg/day)	**C** (%)	**RF** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	1	1	1.2219
Face cream	1540	1	1	0.2406
Hand cream	2160	1	1	0.3375
Fragrances	750	1	1	0.1172
Deodorant (non-spray)	1500	1	1	0.2344
Shampoo	10460	1	0.01	0.0163
Hair conditioner	3920	1	0.01	0.0061
Shower gel	18670	1	0.01	0.0292
Hand wash soap	20000	1	0.01	0.0313
Hair styling products	4000	1	0.1	0.0625
Total				**2.2970**

C = concentration (%); RF = Retention Factor
Daily Systemic Exposure = (Amount × C × RF x dermal absorption)/body weight

- Hair spray (inhalation exposure)

Product type	**Amount** (g/day)	**C** (%)	**Inhalation Rate** (m^3/day)	**Exposure Duration (Zone 1)** (min)	**Exposure Duration (Zone 2)** (min)	**Fraction Inhaled** (%)	**Volume (Zone 1)** (m^3)	**Volume (Zone 2)** (m^3)	**Daily systemic exposure** (mg/kg bw/day)
Hairspray	9.89	1	20	1	20	50	1	10	**0.0332**

Total Daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]
Note - conversion factors of 0.1 [to account for C/Bioavailability as a % and unit conversion (g to mg) ((1/100 × 1/100) × 1000)] and 1440 [to account for mins to day conversion, i.e. 1440 mins/day]

- Household products (Indirect dermal exposure – from wearing clothes)

Product type	**Amount** (g/use)	**C** (%)	**Product Retained (PR)** (%)	**Percent Transfer (PT)** (%)	**Daily systemic exposure** (mg/kg bw/day)
Laundry liquid	230	1	0.95	10	0.0341
Fabric softener	90	1	0.95	10	0.0134
Total					**0.0475**

Daily Systemic Exposure = (Amount × C × PR × PT)/body weight

- Household products (Direct dermal exposure – from wearing clothes)

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	1	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1	1980	1	0.01	0.007	0.0217
Total							**0.0245**

Daily Systemic Exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale factor × dermal absorption)/body weight

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 2.4011 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However it is considered that he combination of conservative hair spray inhalation exposure assessment parameters, (in particular assuming an airspace volume of 2 m^3), and the aggregate exposure form the use of the dermally applied products, (which assumes a conservative 100% absorption rate), is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners).

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 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5.97 mg/L/4 hour; low toxicity
Skin irritation (in vitro: Reconstructed Human Epidermis Test)	irritating
Eye irritation (in vitro)	not corrosive or a severe eye irritant
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 300 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution
No information on the toxicokinetics of the notified chemical was provided. For dermal absorption, molecular weights below 100 Da are favourable for absorption and molecular weights above 500 Da do not favour absorption (ECHA, 2014). Dermal uptake is likely to be moderate to high if the water solubility is between 100-10,000 mg/L and log P values between 1 and 4 also favour dermal absorption (ECHA, 2014). Based on the water solubility (2.16 g/L at 20 °C), partition coefficient (log Pow = 2.69) and the low molecular weight (206.24 Da) 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 if inhaled.

Acute toxicity
The notified chemical was found to have low acute toxicity in rats via the oral, dermal and inhalation routes.

Irritation
Evidence of irritation was observed in an *in vitro* skin irritation study using the Reconstructed Human Epidermis Test Method. Although there was no specific study conducted on the notified chemical to look at its skin corrosion potential, the lack of significant dermal effects seen in the guinea pig maximisation study suggest it is unlikely to be corrosive to the skin.

No prediction could be made on the eye irritation potential of the notified chemical in an *in vitro* eye irritation study using the Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants. The notified chemical was slightly irritating to the eye when tested in rabbits.

Sensitisation
The notified chemical showed no evidence of reactions indicative of skin sensitisation when challenged at 100% in a guinea pig maximisation test.

Repeated dose toxicity
In a 28 day repeat dose study by oral gavage, rats were administered the notified chemical at doses of 30, 300 or 750/500 mg/kg bw/day. The test substance was administrated at 750 mg/kg bw/day at days 1 and 2 and reduced to 500 mg/kg bw/day at days 3-28 as a precautionary measure.

Administration of 750/500 mg/kg/day resulted in the euthanasia of 2 rats (1 male and 1 female) due to the severity of the clinical signs observed, findings were associated with local irritation to the stomach. The combination of these findings indicated that this was an adverse effect level.

At 300 mg/kg/day the findings in the liver, kidney and stomach were observed to a lesser extent than at 750/500 mg/kg/day and in the absence of any deaths or clinical signs, 300 mg/kg/day was considered as the no-observed-adverse effect level (NOAEL).

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study and non-clastogenic in an in vitro mammalian chromosome aberration test.

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*
Skin Irritation (Category 2)	H315 – Causes skin irritation

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):
R38: Irritating to Skin

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Formulation of end use products
Exposure of workers to the notified chemical (in its pure form) may occur during blending operations. The notified chemical skin irritant and a slight eye irritant. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

However, 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.

Beauty care and cleaning professionals
Cleaners and beauty care professionals will handle the notified chemical at ≤ 1% 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
The general public will be repeatedly exposed to the notified chemical during the use in a variety of cosmetic and household products containing the notified chemical at ≤ 1%.

Local effects

The notified chemical is irritating to the skin and slightly irritating to eyes. However at the low proposed end use concentrations skin and eye irritation effects are not expected.

Systemic effects
Members of the public may experience repeated exposure to the notified chemical through the use of the cosmetic and household products (containing the notified chemical at ≤ 1% concentration).

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 2.4011 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 300 mg/kg bw/day, as determined by the study authors in a 28-day repeated dose toxicity study on the notified chemical. Using the abovementioned NOAEL, a MoE of 125 was estimated. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure; therefore, the MoE is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical as a fragrance component in a variety of cosmetic and household products at ≤ 1% is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance formulations for reformulation into finished cosmetic formulations and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. It is estimated by the notifier that a maximum of 0.001% (or up to 10 g) of the notified chemical may be released from accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail. Wastes containing the notified chemical generated during reformulation including equipment wash will be collected and released to sewers in a worst case scenario, or disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic formulations and household end-products.

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated by the notifier that a maximum of 0.003%, or up to 30 g of the notified chemical, may remain in end-use containers once the consumer products are used up. Wastes and residue of the notified chemical in empty containers are likely either to share the fate of the container and be disposed of to landfill, or to be released to sewer when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system through its use in cosmetic formulations and household products, before potential release to surface waters nationwide. Based on the results of a ready biodegradability study, the notified chemical is not considered readily biodegradable (52.3% in 28 days), although it is expected to be ultimately biodegradable. For details of the environmental fate study, please refer to Appendix C. Based on its water solubility and adsorption coefficient (log K_{OC} = 2.0-2.5), release to surface waters may occur as only partial partitioning to sludge and sediment is expected. The notified chemical is not expected to bioaccumulate due to its low partition coefficient (log P_{OW} = 2.69), surfactant properties and ultimate biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile from water based on its vapour pressure (5.9×10^{-4} kPa at 25 °C) and may slowly volatilise to air during use of sewage treatment. The half-life of the notified chemical in air is calculated to be 2.46 h, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation, or disposed of to landfill as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

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	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.606	µg/L
PEC - Ocean:	0.061	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 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.39 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 = 23 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 21.7 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 12 mg/L 72 h E_bC50 = 7.45 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 189 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be harmful to aquatic life. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as “Acute Category 3; Harmful to aquatic life”. Based on the acute toxicity and lack of ready biodegradability, the notified chemical is formally classified as “Chronic Category 3; Harmful to aquatic life with long lasting effects” under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the growth inhibition endpoint for algae. A safety factor of 100 was used given acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
E_rC50 (Algae, 72 h)	12	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	120	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.606	120	0.005
Q – Ocean	0.061	120	0.001

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. Although the notified chemical is not considered readily biodegradable, it is expected to be ultimately biodegradable and is expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/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 changed in appearance during cooling.
Test Facility Firmenich (2013)

Boiling Point Decomposes at 240 °C at 98.0 kPa prior to boiling

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

Density 1,101 kg/m^3 at 20 ± 0.5 °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 5.9×10^{-4} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Test Facility Consilab Gesellschaft für Anlagensicherheit mbH (2014a)

Water Solubility 2.16 g/L at pH 4.1 at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method
Test Facility Dr U Noack-Laboratorien (2014a)

Hydrolysis as a Function of pH Stable at pH ≤ 7
Unstable at pH > 7

Method In-house method (full study report not provided). The stability of the notified chemical was conducted under accelerated conditions of 40 °C over 30 days in buffers at pH 2, 5, 7, 8.5, and 12.

pH	*T (°C)*	*% degradation at 30 days*
2	40	< 10
5	40	< 10
7	40	< 20
8.5	40	> 60
12	40	> 90

Remarks After 5 days under the accelerated conditions of 40 °C the rate of hydrolysis of the notified chemical was less than 10% at pH 2, 5 and 7, and less than 20% at 30 days. This equates to a half-life at 25 °C of $t_{½}$ > 1 year. The rate of hydrolysis of the notified chemical was greater than 10% at pH 8.5 and 12 after 5 days, and reached > 60% hydrolysis at pH 8.5 and > 90% hydrolysis at pH 12 by 30 days. Therefore, it can be concluded that under the conditions of the test, the notified chemical is expected to be hydrolytically stable under acidic and neutral conditions, but is expected to hydrolyse under basic conditions.
Test Facility Firmenich (2013b)

Partition Coefficient (n-octanol/water) log Pow = 2.69

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 (2013a)

Surface Tension 39.46 mN/m at 1 g/L aqueous solution at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Ring Method. The notified chemical was measure as a 1 g/L aqueous solution.
Test Facility	Dr U Noack-Laboratorien (2014b)

Adsorption/Desorption log K_{oc} = 2.0-2.3 at 23.6 °C for soil
log K_{oc} = 2.0-2.5 at 23.6 °C for sewage sludge

Method	OECD TG 121 Adsorption/Desorption (log K_{OC}).
Remarks	HPLC Method
Test Facility	Dr U Noack-Laboratorien (2015)

Flash Point 135 ± 2 °C at 101.3 kPa

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

Autoignition Temperature 370°C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	The test was conducted according to DIN 51794
Test Facility	Consilab Gesellschaft für Anlagensicherheit mbH (2014b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified 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/Crl:CD(SD) albino
Vehicle	Corn oil
Remarks - Method	No deviation form protocol

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	The following clinical signs were noted from approximately 15 minutes after dosing: all females showed underactive behaviour and irregular breathing, 5 showed flat posture, piloeraction and reduced body tone, 4 showed partially closed eye lids and unsteady abnormal gait, 3 showed splayed hindlimbs, fast breathing and reduced body temperature, 1 showed hunched posture and overactive behaviour. Recovery was completed by days 2 or 3.
Effects in Organs	No abnormalities were noted.
Remarks - Results	Satisfactory weight gains were observed in all animals.

CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Huntingdon Life Sciences (2014)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Wistar (RccHan™:WIST)
Vehicle	None
Type of dressing	Semi-occlusive.
Remarks - Method	No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 per sex	2,000	0/2
2	4 per sex	2,000	0/8

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema and crust formation were noted at the test sites of two female animals. Glossy skin was observed at the test site of one female animal.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted.

Remarks - Results	Satisfactory weight gains were observed in all animals except that one female animal showed no gain in bodyweight during the first week with the expected gain during the second week.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Harlan Laboratories Ltd (2014a)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity. EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation).
Species/Strain	Rat/RccHan™:WIST
Vehicle	None
Method of Exposure	Oro-nasal exposure.
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	Mean mass median aerodynamic diameter = 2.63 µm Geometric standard deviation = 2.57 Predicted amount less than 4 µm = 67.3%
Remarks - Method	Minor protocol deviations did not affect the purpose of validity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <mg/L>*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	35.7	5.97 ± 0.25	1 F

LC50	> 5.97 mg/L/4 hours
Signs of Toxicity	During exposure, one male and two female animals exhibited decreased respiratory rate. On removal from the chamber, all animals exhibited decreased respiratory rate. Frequent instances of lethargy and occasional instances of laboured respiration, noisy respiration and coma were also noted. Little or no change in the condition of the animals was noted one hour after exposure. One day after exposure, one female was killed due to still being comatose. This animal also showed decreased respiration rate, laboured respiration, dehydration and pilo-erection. All other animals exhibited decreased respiration rate or increased respiration rate, hunched posture and pilo-erection. Laboured respiration, ataxia, lethargy, dehydration, pallor or extremities and dry eyes (the observation of blinking less than usual with no blinking on contact with the eyes persisted for one day only) were observed in one female animal. Observation gradually reduced over the recovery period until day 8 after exposure when animals appeared normal.
Effects in Organs	One surviving male exhibited dark patches on the lungs. No other macroscopic abnormalities were detected at necropsy amongst animals that survived until the end of 14 day recovery period. At necropsy, pale liver and kidneys were observed in the female animal which was killed during the course of the study.
Remarks - Results	All animals showed bodyweight losses or exhibited no bodyweight gain on the first day after exposure. Bodyweight gains were observed in all animals during the remainder of the recovery period, except that one female animal showed no bodyweight gain from days 1 to 3 after exposure.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY Harlan Laboratories Ltd (2014b)

B.4. Irritation – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method

Vehicle None

Remarks - Method Minor protocol deviations did not affect the purpose of validity of the study.

As the results of the MTT test were unequivocal, 1L-1α analysis was not conducted.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.980	100*	4.7
Test substance	0.080	8.1	1.6
Positive control	0.054	5.5	0.4

OD = optical density; SD = standard deviation

*The mean viability of the negative control issue is set at 100%.

Remarks - Results An assessment showed the test substance was able to directly reduce 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT). The results of the water-killed tissues for quantitative correction of results or for reporting purposes were not used as these results showed a negligible degree of interference due to the direct reduction of MTT occurring.

The acceptance criteria for the positive control, negative control and test substance were considered to be met.

CONCLUSION The notified chemical was irritating to the skin under the conditions of the test.

TEST FACILITY Harlan Laboratories Ltd (2014c)

B.5. Irritation – eye (in vitro)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 438 Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants

Vehicle None

Remarks - Method No significant protocol deviations.

RESULTS

Remarks - Results The ocular reactions observed in eye treated with the test substance were:
-maximal mean corneal swelling: +3% corresponding to the ICE score I (0-5%);
-maximal mean score of corneal opacity: 0.0, corresponding to the ICE class I (0.0-0.5);
-mean score of fluorescein retention: 2.3, corresponding to the ICE class III (1.6-2.5).

The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

CONCLUSION

Although no prediction could be made on the combination of the 3 endpoints tested, the study authors considered that the notified chemical was not corrosive or a severe eye irritant under the conditions of the test. Additional testing (in vitro and/or in vivo) was required to establish a definitive classification.

TEST FACILITY

Phycher Bio Developpement (2014)

B.6. Irritation – eye

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 405 Acute Eye Irritation/Corrosion.
EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	1 F, 2 M
Observation Period	7 days
Remarks - Method	No protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	1.3	1.7	2	< 7 days	0
Conjunctiva: chemosis	0	0.3	1	2	< 7 days	0
Conjunctiva: discharge	0	0.3	0.7	2	< 72 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0.3	1	< 48 hours	0

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

Remarks - Results

No initial pain reaction was noted in any animal following instillation of the test substance. No corneal effects were noted during the study.

One treated eye showed iridial inflammation one and 24 hours after treatment.

Moderate conjunctival irritation was noted in all treated eyes one hour after treatment, in two treated eyes with minimal conjunctival irritation in one treated eye at the 24-hour observation and in one treated eye with minimal conjunctival irritation in one treated eye at the 48-hour observation. Two treated eyes showed minimal conjunctival irritation at the 72-hour observation.

While one treated eye was normal at the 48-hour observation, the other two treated eyes were normal at the 7-day observation.

Body weight gain was as expected with a minor variation in one animal during the study.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Harlan Laboratories Ltd (2014d)

B.7. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation - <Magnusson and Kligman>.
Species/Strain	Guinea pig/Dunkin-Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 100% intradermal: 10, 20, 50, 100% topical: 10, 20, 50, 100%
MAIN STUDY	
Number of Animals	Test Group: 10 F Control Group: 5 F
Vehicle	Olive oil
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
INDUCTION PHASE	Induction Concentration: intradermal: 10% topical: 100%
Signs of Irritation	Dryness was noted in 2 animals and a scab in one animal after the second induction.
CHALLENGE PHASE	
challenge	topical: 100%
Remarks - Method	Minor protocol deviations did not affect the purpose of validity of the study.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	0%	0/10	0/10
	100%	0/10	0/10
Control Group	0%	0/5	0/5
	100%	0/5	0/5

Remarks - Results	No mortality was recorded during the main test. The body weight gain was normal.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Phycher Bio Developpement (2015)

B.8. 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	Rats/Sprague Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	Due to an oversight urinary potassium, sodium and chloride were not measured during the recovery urinalysis investigations. Urinary chloride was considered to have been affected by treatment at week 4, therefore the loss of this data prevented assessment of recovery. If this finding had been present at recovery, in isolation it would have not been considered as adverse, therefore study authors did not consider the loss of this data to affect the overall scientific validity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	30	0
mid dose	5 per sex	300	0
high dose	5 per sex	750/500*	1 per sex
control recovery	5 per sex	0	0
high dose recovery	5 per sex	750/500*	0

*The test substance was administrated at 750 mg/kg bw/day at days 1 and 2 and reduced to 500 mg/kg bw/day at days 3-28 as a precautionary measure.

Mortality and Time to Death

Due to persistent unresponsive behaviour, one female animal and one male animal in the high dose group were euthanised on day 1 and day 5 respectively for welfare reasons.

Clinical Observations

Clinical signs of the dead animals prior to death consisted of unresponsive behaviour, decreased activity, prostrate posture and cold to touch for both animals, unsteady gait for the female animal and irregular breathing and partially closed eyelids for the male animal.

In the high dose group, unsteady gait and decreased activity was noted in the surviving animals a few minutes following dosing and the effect disappeared at the end of the working day for most male and female animals from day 1 to 7. Transient piloerection, partially closed eyelids, unresponsive, swaying and flattened or prostrate posture were noted between days 1 and 6 in a few male and female animals. Transient chin rubbing or salivation noted in female animals was considered by the study authors to be a response to the taste of the test substance and therefore it was not of toxicological importance.

No clinical signs were noted in any animals in the low and mid dose groups.

For surviving animals, there was no effect of treatment on sensory reactivity and grip strength values, motor activity, body weight gain, food consumption and water consumption.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Macroscopic examination of the dead animals showed a pale spleen and distended stomach for both animals, bedding material in the oral cavity for the female animal and dark areas on the stomach and irregular surface of the stomach mucosa for the male animal.

When compared with control values, the haematological examination on surviving animals on day 29 revealed a higher group mean lymphocyte count for treated animals, with the group mean value for male animals in the high dose group showing statistical significance ($p < 0.05$). Most of lymphocyte values were similar to control animals following the recovery period.

Haematology investigations following 28 days of treatment and 15 days of recovery indicated a higher group mean basophil and monocyte count for treated animals when compared to controls with male animals showing statistically significance in the high dose group at the end of recovery period, and then the total remained higher than control animals.

Study authors considered other differences from values for control animals, including those showing statistical significance, were attributed to normal biological variation. These included higher than control mean cell haemoglobin and mean cell volume for female animals in the high dose group following 28 days of treatment and lower than control reticulocyte count and activated partial thromoboplastin time for male animals in the high dose group following 28 days of treatment and two weeks recovery.

In surviving animals, blood chemistry investigations on day 29 revealed a high group mean alanine amino-transferase activity when compared to control animals for both sexes in the mid and high dose groups. The group mean alkaline phosphatase concentration, aspartate amino transferase activity and plasma cholesterol levels were statistically significantly higher than control for treated males in the high dose group. The group

mean plasma potassium ion concentration was higher than control on day 29 for both sexes in the high dose group, especially showing statistical significance ($p < 0.05$) in female animals only. Following 2 weeks recovery these effects became similar to the control animals.

Study authors considered other differences from values for control animals, including those showing statistical significance, were attributed to normal biological variation as these effects were confined to one sex, lacked dose relationship or were not apparent during the treatment phase. These included statistically lower than control sodium concentration for males in the high dose group at the end of the treatment period, a higher than control potassium level for females in the high dose group following 28 days of treatment and a higher than control blood glucose level for females in the high dose group following 28 days of treatment and 2 weeks recovery.

In surviving animals, a higher group mean glucose concentration for all treated groups in both sexes when compared to controls with males and females in mid and high dose groups showing statistical significance was noted in urinalysis investigations in week 4. After 2 weeks of recovery the glucose levels for animals in the high dose group was similar to that of control animals.

Following 4 weeks of treatment, a higher than control group mean chloride concentration was seen for all treated animals, with both sexes in the high dose group showing statistical significance. Due to an oversight this parameter was not assessed at the end of the recovery period.

Study authors considered other differences from values for control animals, including those showing statistical significance, were attributed to normal biological variation as these effects were minor or lacked dose-relationship. These included higher than control sample volume, protein concentration and urinary creatinine concentration for females in the high dose group following 28 days of treatment.

Effects in Organs

Microscopic examination of the dead animals showed a slight increase in cellularity of the spleen for the female animal and decreased cellularity of the red pulp in the spleen and minimal hyperplasia of the non-glandular region of the stomach for the male animal.

For surviving animals, after 4 weeks of the treatment the relative group mean liver weight was marginally but statistically significantly higher than the control for both sexes in the mid and high dose groups. The relative kidney weights were also higher than the control for both sexes in the high dose group, showing statistical significance ($p < 0.05$) in female animals only. After 2 weeks of recovery the relative liver weight for female animals remained higher than the control. The relative kidney weights were similar to control for both sexes.

Minimal hyperplasia of the non-glandular epithelium of the stomach was seen in one male animal from each of the mid and high dose group. Slight hyperplasia seen in one male animal in the low dose group was associated with slight ulceration and inflammation and minimal oedema, and the same effect seen in one female animal in the high dose group was linked with slight hyperkeratosis and minimal parakeratosis.

Remarks – Results

For surviving animals, no test substance related lesions were noted in the macroscopic examination conducted after 28 days of treatment and a two week recovery period.

There was evidence of adaptive changes in the liver in the high dose group and to a lesser extent in the mid dose group. The increased cholesterol, alanine amino-transferase, alkaline phosphatase and aspartate amino-transferase levels, and increased adjusted liver weight were indicative of increased activity in the liver. Orally administered substances are metabolised by the liver, therefore this increase in activity was considered as a normal adaptive response following administration of a test substance. There was general evidence of recovery and no histopathological changes were noted in the liver.

The increased adjusted kidney weight for females, and to a lesser extent males, in the high dose group was considered to be associated with the increase in plasma potassium, urinary glucose and chloride levels. There was full recovery with no histopathological changes being noted in the kidney.

The histopathological examinations showed minimal or slight hyperplastic and/or degenerative/inflammatory changes in the non-glandular region of the stomach from individual males in each treated group and females at in the high dose group. This was indicative of local irritation, being consistent with the macroscopic stomach

findings at higher dose levels in the 7-day preliminary study conducted in the same laboratory. For some individuals, including one male animal in each test substance group, , there was a correlation between this irritation and the increased lymphocyte count at the end of the treatment period, with the increased basophil and monocyte count at the end of the recovery period being a continuation of the response to local irritation insult.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 300 mg/kg bw/day in this study, based on the findings at this dose level were less severe than at 750/500 mg/kg bw/day and there were no deaths or clinical signs.

TEST FACILITY Hungtingdon Life Sciences (2015)

B.9. 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.
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, 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: 0 – 5,000 µg/plate b) Without metabolic activation: 0 – 5,000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	No protocol deviations. Test 1 is the range-finding test and test 2 is the main test. Not all test levels were used for all *Salmonella* and *E. Coli* strains.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 1,500 µg	> 5,000	negative
Test 2	≥ 15 µg	> 5,000	negative
Present			
Test 1	≥ 150 µg	> 5,000	negative
Test 2	≥ 5 µg	> 5,000	negative

Remarks - Results

In test 1, reduction in the growth of the bacterial background lawn was visible in all strains initially from 5 µg/plate (TA100 and TA1535), 150 µg/plate (TA98 and TA1537) and 500 µg/plate (WP2uvrA), without metabolic activation and from 5 µg/plate (TA100 and TA1535), 150 µg/plate (TA1537) and 500 µg/plate (TA98 and WP2uvrA), with metabolic activation. Similar results were observed in test 2.

A small but statistically significant increase in revertant colony frequency was observed in the TA98 with metabolic activation at 50 µg in the main test. As there was no dose response relationship or reproducibility and the value was within the historical control range the study authors considered it to be of no biological relevance. No other statistically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, either with or without metabolic activation.

No test substance precipitate was observed on the plates at any of the doses tested in either the presence or absence of S9-mix.

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 Ltd (2014e)

B.10. Genotoxicity – in vitro

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
Cell Type/Cell Line	Lymphocytes/peripheral
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks - Method	Minor protocol deviations did not affect the purpose of validity of the study. Cell growth inhibition test was conducted to determine the maximum dose level for tests 1 and 2.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 30, 60, 120, 160*, 200*, 240*	4	24
Test 2	0*, 30, 60*, 120, 160*, 200*, 240*	4	24
Present			
Test 1	0*, 30, 60, 120*, 160*, 200*, 240*	4	24
Test 2	0*, 30, 60, 120*, 160*, 200*, 240	4	24

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:* *Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 240	> 240	negative
Test 2	≥ 240	> 240	negative
Present			
Test 1	≥ 240	> 240	negative
Test 2	≥ 240	> 240	negative

Remarks - Results In both tests 1 and 2, no precipitate or haemolysis was observed at the end of exposure in either exposure group.

Test 1
The test substance induced a statistically significant increase in the frequency of cells with chromosome aberrations in the absence of metabolic activation at 240 µg/mL being accompanied by optimum toxicity. The test substance also induced an increase in the frequency of cells with chromosome aberrations in the presence of metabolic activation at 240 µg/mL, although this was not considered to be statistically significant by study authors and it was accompanied by excessive toxicity (mitotic index value of 31%).

The test substance did not induce a statistically significant increase in the number of polyploid cells at any dose level in either of the exposure groups.

	Test 2 The test substance did not induce any statistically significant increases in the frequency of cells with chromosome aberrations either in the absence or presence of metabolic activation. The test substance did not induce a statistically significant increase in the number of polyploid cells (one incidence of endoreduplication was noted) at any dose level in either of the exposure groups. As the statistically significant increase in the frequency of cells with chromosome aberrations in the absence of metabolic activation at 240 µg/mL in test 1 was not replicated in the presence of metabolic activation or in test 2 the study authors considered it to be of no toxicological significance. The positive and vehicle control values confirmed the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	Harlan Laboratories Ltd (2015)

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.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Total Organic Carbon (TOC)
Remarks - Method	No significant deviation in protocol was reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	2.2	7	62.5
14	16.7	14	77.9
21	38.5	21	82.2
28	52.3	28	88.8

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 7 days (62.5%) and reached 88.8% degradation by 28 days. Therefore, the test indicates the suitability of the inoculums. As the test substance is surface active, the 10-day window is not applicable. The test substance attained 52.3% degradation by 28 days, and a degradation plateau was not achieved. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 B) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Guangdong Detection Center of Microbiology (2014a)

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.
Species	*Danio rerio* (Zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	123 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The definitive test was conducted at nominal concentrations of 9.53, 17.1, 30.9, 55.6, and 100 mg/L of the test substance. No significant deviation in protocol was reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*

Control	Control	10	0	0	0	0	0
9.53	9.22	10	0	0	0	0	0
17.1	16.4	10	0	0	0	0	0
30.9	ND	10	0	100	100	100	100
55.6	ND	10	100	100	100	100	100
100	ND	10	100	100	100	100	100

ND: not determined

LC50	23.0 mg/L at 96 hours.
NOEC	17.1 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 96 h test period. The actual concentrations of the test substance were measured on samples taken at 0, 24, 72, and 96 hours during the 96 h test period. Samples were extracted using ethyl acetate and stored at 4 °C. However, concentration measurements were conducted outside of the 4 days of the test period, although this deviation was not deemed to have had a significant impact on the validity or the integrity of the study. The measured concentrations of the test substance were within 20% difference of the nominal test concentrations, therefore the nominal test concentrations are considered valid. The 96 h LC50 and NOEC for fish were determined to be 23.0 mg/L and 17.1 mg/L, based on nominal concentrations.
CONCLUSION	The notified chemical is considered to be harmful to fish.
TEST FACILITY	Guangdong Detection Center of Microbiology (2014b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	160-180 mg $CaCO_3$/L
Analytical Monitoring	GC-MS
Remarks - Method	The definitive test was conducted at nominal concentrations of 2.5, 5, 10, 20, 40, and 80 mg/L of the test substance. A total of 20 daphnids (5 daphnids/replicate across 4 replicates) were used. No significant deviation in protocol was reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
2.5	2.23	20	0	0
5	4.46	20	10	20
10	9.91	20	5	25
20	17.6	20	15	40
40	43.2	20	75	100
80	82.0	20	85	100

EC50	21.7 mg/L (95% CI 19.5-28.5 mg/L) at 48 hours
NOEC	Not determined
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 48 h test period. The actual concentrations of the test substance were measured at 0, 24 and 48 hours

during the 48 h test period. As the measured concentrations of the test substance were within 20% difference of the nominal test concentrations, therefore the nominal test concentrations are considered valid. The 48 h EC50 for *Daphnia* was determined to be 21.7 mg/L, based on nominal concentrations.

CONCLUSION The notified chemical is considered to be harmful to aquatic invertebrates.

TEST FACILITY Dr U Noack-Laboratorien (2014c)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
- Species *Pseudokirchneriella subcapitata* (green alga)
- Exposure Period 72 hours
- Concentration Range Nominal: 3.125-100 mg/L; Actual: 2-41 mg/L
- Auxiliary Solvent None
- Water Hardness 0.24 mmol Ca+Mg/L
- Analytical Monitoring GC-MS/MS
- Remarks - Method The definitive test was conducted at nominal concentrations of 3.125, 6.25, 12.5, 25, and 50 mg/L of the test substance (corresponding to measured concentrations of 2.00, 4.38, 9.29, 19.6, and 41.0 mg/L, respectively). No significant deviation in protocol was reported.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
7.45 (95% CI 6.05-8.85)	2.00	12.0 (95% CI 11.1-13.7)	2.00

Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the test substance were at 0 and 72 hours within the 72 h test period. The test solutions were not renewed during the 72 h test period. The 72 h E_rC50, E_bC50, and NOEC were determined to be 12 mg/L, 7.45 mg/L, and 2 mg/L, respectively, based on the geometric mean measured concentrations.

CONCLUSION The notified chemical is considered to be harmful to algae.

TEST FACILITY Dr U Noack-Laboratorien (2014d)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.
- Inoculum Activated sludge
- Exposure Period 3 hours
- Concentration Range Nominal: 3.2-1000 mg/L; Actual: Not determined
- Remarks – Method No significant deviation in protocol was reported. Copper (II) sulphate pentahydrate was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.

RESULTS

IC50	189 mg/L (95% CI 165-219 mg/L) at 3 hours
NOEC	10 mg/L at 3 hours
Remarks – Results	All validity criteria for the test were satisfied. The 3 h IC50 was determined to be 189 mg/L, based on nominal concentrations.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	Dr U Noack-Laboratorien (2014e)

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