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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Tillenal

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (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 Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Sustainability, Environment, Water, Population and Communities.

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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TABLE OF CONTENTS

SUMMARY 3
CONCLUSIONS AND REGULATORY OBLIGATIONS 3
ASSESSMENT DETAILS 5
1. APPLICANT AND NOTIFICATION DETAILS 5
2. IDENTITY OF CHEMICAL 6
3. COMPOSITION 6
4. PHYSICAL AND CHEMICAL PROPERTIES 6
5. INTRODUCTION AND USE INFORMATION 7
6. HUMAN HEALTH IMPLICATIONS 7
6.1. Exposure Assessment 7
6.1.1. Occupational Exposure 7
6.1.2. Public Exposure 8
6.2. Human Health Effects Assessment 9
7. ENVIRONMENTAL IMPLICATIONS 12
7.1. Environmental Exposure & Fate Assessment 12
7.1.1. Environmental Exposure 12
7.1.2. Environmental Fate 12
7.1.3. Predicted Environmental Concentration (PEC) 13
7.2. Environmental Effects Assessment 13
7.2.1. Predicted No-Effect Concentration 14
7.3. Environmental Risk Assessment 14
APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES 15
APPENDIX B: TOXICOLOGICAL INVESTIGATIONS 18
B.1. Acute toxicity – oral 18
B.2. Acute toxicity – dermal 18
B.3. Irritation – skin (in vitro) 19
B.4. Irritation – skin 19
B.5. Irritation – eye (in vitro) 20
B.7. Skin sensitisation – mouse local lymph node assay (LLNA) 22
B.8. Repeat dose toxicity 22
B.9. Genotoxicity – bacteria 23
B.10. Genotoxicity – in vitro 24
APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS 26
C.1. Environmental Fate 26
C.1.1. Ready biodegradability – Study 1 26
C.1.2. Ready biodegradability – Study 2 26
C.2. Ecotoxicological Investigations 27
C.2.1. Acute toxicity to fish 27
C.2.2. Acute toxicity to aquatic invertebrates 28
C.2.3. Algal growth inhibition test 29
C.2.4. Inhibition of microbial activity 29
BIBLIOGRAPHY 31

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS SUBSTANCE	INTRODUCTION VOLUME	USE
LTD/1617	Firmenich Limited	Tillenal	Yes	<1 tonne per annum	Fragrance ingredient in cosmetic and household products

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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 4)	H227 – Combustible liquid
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 2)	H315 – Causes skin irritation
Eye damage (Category 1)	H318 – Causes serious eye damage
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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

R22 Harmful if swallowed
R38 Irritating to skin
R41 Risk of serious damage to eyes
R43 May cause sensitisation by skin contact

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

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

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

When used at ≤1.0% in fine fragrances, ≤0.1% in other leave-on cosmetic products, ≤0.5% in rinse-off cosmetic products and ≤0.9% in 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 assessed 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): H302 – Harmful if swallowed
  - Skin Irritation (Category 2): H315 – Causes skin irritation
  - Eye damage (Category 1): H318 – Causes serious eye damage
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

- The following should be used for products/mixtures containing the notified chemical:
  - Conc. ≥25%: H302, H315, H317, H318
  - ≥10% Conc. <25%: H315, H317, H318
  - ≥3% Conc. <10%: H317, H318
  - ≥1% Conc. <3%: H317, H319*

  *H319 – Causes serious eye irritation

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

Health Surveillance

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

CONTROL MEASURES
Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following isolation and engineering controls 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:
  - Coveralls, impervious gloves, goggles

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must 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 ≤1.0% in fine fragrances, ≤0.1% in other leave-on cosmetic products, ≤0.5% in rinse-off cosmetic products and ≤0.9% in household products.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(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 1.0% in fine fragrances, 0.1% in other leave-on cosmetic products, 0.5% in rinse-off cosmetic products and 0.9% in household products.

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of cosmetic and household products, or is likely to change 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: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, residual monomers, 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
USA (2010)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Tillenal

MOLECULAR WEIGHT
<500 Da

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

3. COMPOSITION

DEGREE OF PURITY >75%

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	Decomposition from ~222 °C at 97.9 kPa	Measured
Density	919 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.1 x 10^{-2} kPa at 25 °C	Measured
Water Solubility	0.138 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	>28% after 28 days (40 °C, pH 2-12)	Measured
Partition Coefficient (n-octanol/water)	log Kow = 3.30	Measured
Surface Tension	54.0 mN/m at 22.2 ± 0.5 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.60	Measured
Dissociation Constant	Not determined	Contains no readily dissociable functional groups
Flash Point	91 ± 2 °C at 101.3 kPa (closed cup)	Measured
Autoignition Temperature	228 ± 5 °C	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidative properties.

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 4)	H227 – Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as a component of compounded fragrances.

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 MANUFACTURER/RECIPIENTS
Firmenich Ltd

TRANSPORTATION AND PACKAGING
The fragrance preparations containing the notified chemical (at ≤10% concentration) will be imported in tightly closed lacquered drums, typically of 180 kg size, but also 100, 50, 25, 10 or 5 kg. The drums will be transported by road from the wharf or airport of entry to the Firmenich Ltd warehouse for storage and then distributed to reformulation sites. The end-use products will be packaged in containers suitable for retail sale.

USE
The notified chemical is intended to be used as a component of fragrances for a variety of cosmetic and household products (proposed usage concentration: ≤1.15% concentration in fine fragrances, ≤2.5% in other cosmetic products and ≤5% in household products).

OPERATION DESCRIPTION
The procedures for incorporating the imported fragrance preparations (containing ≤10% notified chemical) into end-use products will likely vary depending on the nature of the cosmetic and personal care/household products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes.

The finished products containing the notified chemical 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 workers may come into contact with the notified chemical, as a component of the imported fragrance preparations (≤10% concentration) or end-use products (≤5% concentration), only in the event of accidental rupture of containers.

During reformulation, dermal, ocular and inhalation exposure of workers to the notified chemical (at ≤10% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as coveralls, safety glasses and impervious gloves.

Exposure to the notified chemical in end-use products (at ≤5% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons) or in the cleaning industry. 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 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 ≤5% concentration) through the use of the household products and the 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 and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2010; Cadby *et al.*, 2002; SDA, 2005). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes (European Commission, 2003). For the inhalation exposure assessment (European Commission, 2003; SDA, 2005), an adult inhalation rate of 23 m^3/day (enHealth, 2004) was used and it was assumed that the bioavailability of the notified chemical via the inhalation route is 100%. An adult bodyweight of 60 kg was used for calculation purposes.

- Cosmetic products (Dermal exposure):

Product type	**Amount** (mg/day)	**C** (%)	**RF** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	2.500	1	3.26
Face cream	1540	2.500	1	0.64
Hand cream	2160	2.500	1	0.90
Fine fragrances	750	1.150	1	0.14
Deodorant spray	1430	2.500	1	0.60
Shampoo	10460	2.500	0.01	0.044
Conditioner	3920	2.500	0.01	0.016
Shower gel	18670	2.500	0.01	0.078
Hand soap	20000	2.500	0.01	0.083
Hair styling products	4000	2.500	0.1	0.17
Total				5.93

C = concentration (%); RF = retention factor.

Daily systemic exposure = Amount x C x RF x dermal absorption /body weight

- 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	5	0.95	10	0.18
Fabric softener	90	5	0.95	10	0.07
Total					0.25

Daily systemic exposure = Amount x C x PR x PT x dermal absorption /body weight

- Household products (Direct dermal exposure):

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	5	1980	0.01	0.01	0.007	0.0017
Dishwashing liquid	3	5	1980	0.009	0.01	0.03	0.013
All-purpose cleaner	1	5	1980	1	0.01	0.007	0.12
Total							0.13

Daily systemic exposure = Frequency x C x Contact area x Product Use Concentration x Film Thickness on skin x Time Scale Factor x dermal absorption /body weight

- Cosmetic products (Inhalation exposure):

Product type	Frequency (use/day)	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration (mins)	Airspace volume (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	2	10	2.5	23	15	2	1.00

C = concentration.
Daily systemic exposure = Frequency x Amount x C x Inhalation rate x Exposure duration x bioavailability via the inhalation route/(Airspace volume x 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 7.3 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 the combination of the conservative hair spray inhalation exposure assessment parameters, in particular assuming an airspace volume of 2 m^3, and the aggregate exposure from 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 table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity (fixed dose method)	LD50 300-2000 mg/kg bw; harmful
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw; low toxicity
Skin irritation (in vitro)	borderline non-irritating
Rabbit, skin irritation	irritating
Eye irritation (in vitro)	non-irritating
Eye irritation – rabbit enucleation eye test	severely irritating
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation
Rat, repeat dose oral gavage toxicity - 28 days	NOAEL 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic

Genotoxicity – *in vitro* mammalian chromosome aberration	non genotoxic

Toxicokinetics, metabolism and distribution.
Based on the water solubility (0.138 g/L at 20 ºC), partition coefficient (log K_{ow} = 3.30) and the low molecular weight (<500 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are expected to occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
The notified chemical was found to be harmful in an acute oral toxicity study in rats. Hunched posture, lethargy, ataxia, pilo-erection, decreased respiratory rate, dehydration and hypothermia were noted in the single animal treated at 2000 mg/kg bw. This animal was sacrificed after 1 day of treatment for humane reasons. Signs of systemic toxicity noted in the animals treated at 300 mg/kg bw included hunched posture (4/5 animals) and laboured respiration (1 animal). The animals treated at 300 mg/kg bw recovered within 1 day of dosing.

The notified chemical was found to have low acute dermal toxicity in a study in rats.

No acute inhalation toxicity data were provided for the notified chemical.

Irritation.
An in vitro skin irritation study conducted using a reconstituted human epidermis model (EpiSkin), indicated that the notified chemical was borderline non-irritating. For this reason an irritation study in rabbits was also performed. The notified chemical was determined to be irritating to the skin of rabbits, with well-defined erythema and slight oedema noted. Slight desquamation was noted in all animals at the end of the observation period.

An in vitro eye irritation study conducted using a reconstituted human corneal epithelium model (SkinEthic) indicated that the notified chemical was non-irritating to the eyes. However, the notified chemical was determined to be a severe eye irritant in a rabbit enucleation eye test, with corneal swelling, sloughing and severe corneal opacity noted in treated eyes. Slight to moderate fluorescein uptake was also noted. The effects continued to worsen over the observation period and were most severe after 4 hours (the last observation). As the notified chemical was considered to have the potential to cause severe ocular irritancy, an in vivo eye irritation study was not conducted.

Sensitisation.
The notified chemical was found to be a skin sensitiser in mice (Local Lymph Node Assay; stimulation indices of 2.66, 2.67 and 6.22 at 25, 50 and 100%, respectively). The EC_3 value was calculated to be 54.6%.

Repeated Dose Toxicity
A 28 day repeat dose study by oral gavage was conducted in rats. There were no overt clinical signs of toxicity noted for animals at up to 300 mg/kg bw/day. However, organ weight and histopathological changes were noted in animals treated at this dose.

There were no treatment related macroscopic findings in any organ at necropsy. However, absolute and relative liver and kidney weights were increased in males in the low, mid and high dose groups and females in the high dose group only. While liver weights returned to normal following the recovery period, kidney weights remained elevated for males receiving 300 mg/kg bw/day (the only dose measured in the recovery group). However, the study authors deemed the organ weight effects in both sexes to be non-adverse due to increased water intake, resulting in an adaptive response in organ weights.

Gastro-intestinal tract lesions and inflammation were noted in males receiving 300 mg/kg bw/day. Chronic ulceration was also noted at the conclusion of the study (following the recovery period) in one animal. These effects were attributed to the notified chemical. Based on the adverse gastro-intestinal results of this study, a NOAEL of 150 mg/kg bw/day was derived.

Mutagenicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not 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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 2)	H315 – Causes skin irritation
Eye damage (Category 1)	H318 – Causes serious eye damage
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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

R22 Harmful if swallowed
R38 Irritating to skin
R41 Risk of serious damage to eyes
R43 May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation

Exposure of workers to the notified chemical (at ≤10% concentration) may occur during blending operations. While the notified chemical is considered to be harmful to human health via the oral route, ingestion is unlikely under the occupational settings described. The notified chemical is considered to be a skin and eye irritant and skin sensitiser. In addition, harmful effects following inhalation exposure to the notified chemical cannot be ruled out. Therefore, 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 ≤5% 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

Repeated-dose toxicity

Members of the public may experience repeated exposure to the notified chemical (at ≤5% concentration) through the use of the cosmetic and household products.

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 7.3 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 150 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on the notified chemical. A MoE value ≥300 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure (noting that the NOAEL was derived from a 28-day study). Using the abovementioned NOAEL, a MoE of 21 was estimated, which is considered to be unacceptable.

Reducing the concentration of the notified chemical in fine fragrances to 1.0%, all other leave-on cosmetic products to 0.1%, rinse-off cosmetic products to 0.5% and household products to 0.9% allows recalculation of the combined internal dose to 0.5 mg/kg bw/day. An acceptable MoE of 300 is then estimated.

Irritation

The notified chemical is considered to be a skin irritant and cause serious damage to eyes. Skin irritation effects are not expected from use of the notified chemical at the revised (lowered) concentrations in cosmetic and

household products. However, the potential for eye irritation (namely, from use of household products and fine fragrances, which will contain a higher concentration of the notified chemical) is of concern.

Ocular exposure is only expected to occur in the unlikely event of an accident, and, in the case of household products, the products may be diluted with water at the time of eye contact. The potential for eye irritation may be further minimised by the inclusion of appropriate labelling and directions for use to warn against eye contact.

Sensitisation
The notified chemical is considered to have the potential to cause skin sensitisation. Methods for the quantitative risk assessment of dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using a fine fragrance (containing 1.0 % notified chemical) as an example product that may contain the notified chemical, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 37.5 μg/cm^2 (Cadby *et al.*, 2002). When tested in an LLNA study, the notified chemical was a skin sensitiser with an EC_3 value of 54.6%. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 41.8 μg/cm^2. In this instance, the factors employed included an interspecies factor (3.16), intraspecies factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of >300 (300 used for calculations).

As the AEL>CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example of a leave-on cosmetic product) at ≤1.0% concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level from other leave on cosmetic products (containing ≤0.1% notified chemical), rinse-off products (containing ≤0.5% notified chemical) and household products (≤0.9% notified chemical), by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤1.0% in fine fragrances, ≤0.1% in other leave-on cosmetic products, ≤0.5% in rinse-off cosmetic products and ≤0.9% in household products, 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 preparations for local reformulation into a variety of consumer products (cosmetics and household products). Release during reformulation in Australia is expected to arise from spills (0.1%), formulation equipment cleaning (no release estimate as cleaning water is recycled) and residues in import containers (0.1%). Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill. Import containers will either be recycled or disposed of through an approved waste management facility. Therefore, up to 0.2% of the import volume is estimated to be released to landfill as a result of reformulation in Australia.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to sewers in domestic situations across Australia as a result of its use in cosmetic and domestic products, which are either washed off the hair and skin of consumers, or disposed of following cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated that a maximum of 3% of the consumer products containing the notified chemical will remain in end-use containers. These will be disposed of through domestic garbage disposal and will enter landfill or be recycled.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before

potential release to surface waters on a nationwide basis. The submitted biodegradation studies on the notified chemical indicate that the notified chemical is not expected to be rapidly degraded in sewage treatment plants (STPs). In STPs the notified chemical is expected to be partially removed from influent by adsorption to sludge and a portion may be released to surface waters. The notified chemical is not considered to be bioaccumulative based on its measured log Kow (< 4.2). A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have medium mobility based on its estimated soil adsorption coefficient (log K_{oc} = 2.60). In the aquatic and soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is expected to be volatile and may volatilise to air during use or STP processes. The half-life of the notified chemical in air is calculated to be 1.1 hours based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

7.1.3. Predicted Environmental Concentration (PEC)

Since most of the notified chemical will be washed into the sewer, under a worst case scenario, assuming no removal of the notified chemical in sewage treatment plants (STPs), the resultant Predicted Environmental Concentration (PEC) in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	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:	0.61	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 0.606 µg/L may potentially result in a soil concentration of approximately 4.039 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 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 = 3.1 mg/L	Toxic to fish
Daphnia Toxicity (48 h)	EC50 = 2.5 mg/L	Toxic to aquatic invertebrates
Algal Toxicity (72 h)	E_rC50 = 3.8 mg/L	Toxic to algae
	NOEC = 0.18 mg/L	Toxic to algae with long lasting effects
Inhibition of Bacterial Respiration (3 h)	IC50 = 150 mg/L	Not expected to be inhibitory to bacterial respiration < 150 mg/L

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is acutely toxic to fish, aquatic invertebrates and algae, and is formally classified as 'Acute Category 2: Toxic to aquatic life'. One adequate chronic toxicity endpoint was available (algal NOEC).

Therefore, the long-term classification for the notified chemical was determined based on the most stringent outcome of the long-term hazard classification using either the acute or chronic endpoints. Both classification methods resulted in the same long-term classification. The notified chemical is therefore formally classified under the GHS as 'Chronic category 2; Toxic to aquatic life with long lasting effects'.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the acute daphnia toxicity of the notified chemical and an assessment factor of 100 as measured acute endpoints are available for three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
48 h EC50 (daphnia)	2.5	mg/L
Assessment Factor	100	
PNEC:	25	µg/L

7.3. Environmental Risk Assessment

Based on the above PEC and PNEC values, the following Risk Quotient (Q) has been calculated:

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	25	0.024
Q - Ocean	0.061	25	0.0024

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 based on its annual importation quantity. The notified chemical is expected to have a low potential for bioaccumulation. Therefore, on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic 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 ºC

Method	OECD TG 102 Melting Point/Melting Range. EC Directive 440/2008/EEC A.1 Melting/Freezing Temperature.
Remarks	Determined by placing a test tube containing the test substance in a dry ice/isopropanol bath until the temperature of the substance reached ~-20 ºC. The test substance did not show any indication of freezing.
Test Facility	Firmenich (2010a)

Boiling Point Decomposition from ~222 ºC at 97.9 kPa

Method	OECD TG 103 Boiling Point. EC Directive 440/2008/EEC A.2 Boiling Temperature.
Remarks	Determined according to the Siwoloboff method. The test substance decomposed prior to boiling [decomposition confirmed by differential scanning calorimetry (DSC)].
Test Facility	Firmenich (2010a)

Density 919 kg/m^3 at 20 ± 5 ºC

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Determined using the oscillating density meter method
Test Facility	Firmenich (2010a)

Vapour Pressure 1.1 x 10^{-2} kPa at 25 ºC

Method	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Determined using the gas saturation method.
Test Facility	Harlan (2010a)

Water Solubility 0.138 g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method. Test substance was added to Millipore water in three flasks and shaken at approximately 30 °C for 8 hours. Following shaking the flasks were left to stand at 20 °C for 24 hours to allow the mixture to settle. Aliquots of the water solution (excluding undissolved material) were taken 24, 48, and 72 hours after the initial shaking, filtered through a 45 µm filter and analysed by HPLC. The pH of each solution was measured and were all found to be 4.5.
Test Facility	Firmenich (2010a)

Hydrolysis as a Function of pH ≥ 28% after 28 days (40 °C, pH 2-12)

Method In-house

pH	*T (°C)*	*% hydrolysis after 5 days**	*% hydrolysis after 28 days**
2	40	10	30
5	40	15	32
7	40	10	28
8.5	40	20	54
12	40	98	100

*Approximate values read from graph

Remarks Test substance (200 – 300 ppm) was dissolved in in buffer solutions (types A, C, D, F and

I: Reference Handbook of Chemistry and Physics) containing 1% non-ionic surfactant (Arkopal N 150) and put into storage in an oven at 40 °C over 28 days. Aliquots of test solution were extracted with organic solvent (typically cyclohexane or ethyl acetate) on a regular basis throughout the test and analysed by GC-FID. The rate of hydrolysis was approximately the same at pH 2-7 and increased markedly at pH 8.5 and 12. Hydrolysis was approximately 10% or more after 5 days at 40 ºC across the tested pH range (2-12), indicating the notified chemical has the potential to hydrolyse under environmental conditions.

Test Facility Firmenich (2011a)

Partition Coefficient (n-octanol/water) log Kow = 3.30

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.

Remarks HPLC method. The elution time of the test substance was measured. By comparison to elution times of reference compounds with known log Kow values (range 2.10 – 4.00), the log Kow of the notified chemical was determined by interpolation.

Test Facility Firmenich (2010a)

Surface Tension 54.0 mN/m at 22.2 ± 0.5 ºC

Method EC Directive 440/2008/EEC A.5 Surface Tension.

Remarks Concentration: 90% saturation solution contained 0.128 g/L.
The test material was considered to be a surface active material (but not significantly surface-active).

Test Facility Harlan (2010b)

Adsorption/Desorption log K_{oc} = 2.60

Method EC Council Regulation No 440/2008 C.19 Adsorption Coefficient

Remarks HPLC Method. The adsorption coefficient was determined by interpolation from a calibration curve constructed from known standards (log K_{oc} range 1.25 – 5.63) in accordance with the guidelines above.

Test Facility Harlan (2010b)

Flash Point 91 ± 2 ºC at 101.3 kPa

Method EC Directive 440/2008/EEC A.9 Flash Point.

Remarks Determined using a closed cup equilibrium method.

Test Facility Firmenich (2010b)

Autoignition Temperature 228 ± 5 ºC

Method EC Directive 440/2008/EEC A.15 Auto-Ignition Temperature (Liquids and gases)

Remarks Determined by heating aliquots of the test material in a flask and observing any ignition.

Test Facility Harlan (2010b)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.

Remarks Observation of functional groups that would imply explosive properties.

Test Facility Harlan (2010b)

Oxidizing Properties Predicted negative

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).

Remarks	Observation of functional groups that would imply oxidising properties.
Test Facility	Harlan (2010b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Method.
Species/Strain	Rat/Wister (HsdRccHan)
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	1F	2000	1/1
II	1F	300	0/1
III	4F	300	0/3

LD50	Between 300 and 2,000 mg/kg bw
Signs of Toxicity	Hunched posture was noted in all but one animal. In addition, signs noted in the Group I treated animal included lethargy, ataxia, pilo-erection, decreased respiratory rate, dehydration and hypothermia. Laboured respiration was found in one animal in group III. Surviving animals recovered within 1 day of dosing.
Effects in Organs	None
Remarks - Results	The animal treated at 2000mg/kg bw was killed for humane reasons 1 day after dosing.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	Harlan (2009a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Wister (HsdRccHan)
Vehicle	None
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M	2000	0/5
2	5F	2000	0/5

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema was observed in 4/10 animals during the observation period. The responses were not evident until at least day 3 post treatment and cleared by day 7. Additionally, loss of skin elasticity, brown discolouration, scabs and slight desquamation were noted in 7 animals (evident between days 2-6 post-treatment).
Signs of Toxicity - Systemic	None
Effects in Organs	None
Remarks - Results	The body weight of 1 female was reduced after 1 week, but recovered in the second week, post treatment.

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

TEST FACILITY Harlan (2010d)

B.3. Irritation – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method
EpiSkin™ Reconstituted Human Epidermis Model

Vehicle None

Remarks - Method The test substance (10 µL) was applied to the tissues in triplicate. Following 15 minute exposure periods, the tissues were rinsed and then incubated at 37 °C for approximately 42 hours.

Following treatment with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.3 mg/mL], the tissues were incubated at 37 °C for 3 hours.

Positive (sodium dodecyl sulphate; 5%) and negative (phosphate buffered saline) controls were run in parallel with the test substance. As the tes substance was shown to directly reduce MTT, additional controls were included to detect and correct for the test substance interference

The optical densities were determined at 540 nm.

RESULTS

Test Material	*Mean OD_{540} of triplicate tissues*	*± SD of OD_{540}*	*Relative mean viability (%)*	*± SD of relative mean viability (%)*
Negative Control	0.877	0.059	100*	6.68
Positive Control	0.041	0.007	4.7	0.82
Test Substance	0.443	0.093	50.5	10.6

OD = optical density; SD = standard deviation
*The mean viability of the negative control tissues is set as 100%.

Remarks - Results The relative mean viability of the test substance treated tissues was 50.5±10.6% after a 15-minute exposure period. The test substance results were corrected for direct reduction of MTT by 0.050.
The positive and negative controls gave satisfactory results, confirming the validity of the test system.
A mean tissue viability of >50% is considered as non irritating. The notified chemical is borderline by this definition.

CONCLUSION The notified chemical was considered to be borderline non-irritating to the skin.

TEST FACILITY Harlan (2010l)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain Rabbit/New Zealand White

Number of Animals 2

Vehicle None

Observation Period 14 days

Type of Dressing Semi-occlusive

Remarks - Method No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Erythema/Eschar	2	2	2	<14 days	0
Oedema	2	2	2	<14 days	0

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

Remarks - Results: Well-defined erythema, slight oedema, epidermis discolouration and loss of flexibility/elacticity were noted at up to the day 3 observation. Crust formation prevented evaluation at the treatment sites of both animals at day 7. All effects, except slight desquamation in both animals were resolved by the day 14 observation.

CONCLUSION: The notified chemical is irritating to the skin.

TEST FACILITY: Harlan (2010e)

B.5. Irritation – eye (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: Determination of Ocular Irritation Potential Using the SkinEthic Reconstituted Human Corneal Epithelium Model

Remarks - Method: The test substance (30 µL) was applied to the tissues in triplicate. Following 10 minute exposure periods, the tissues (2/group, with the others being retained for histopathology if necessary) were rinsed and then treated with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.5 mg/mL; incubation period of 3 hours at 37 °C]. Following extraction, the optical densities were determined (540 nm).

Positive (sodium dodecyl sulphate; 1%) and negative controls were run in parallel with the test substance.

The test substance was considered by the study authors to be an irritant if the relative mean tissue viability was <60%.

Under the conditions of a per-test that was conducted, the test substance was shown not to directly reduce MTT.

RESULTS

Test Material	*Mean OD_{540} of duplicate tissues*	*Relative mean viability (%)*
Negative Control	0.951	100*
Positive Control	0.371	39.0
Test Substance	0.808	85.0

OD = optical density
*The mean viability of the negative control tissues is set as 100%.

Remarks - Results: The relative mean viability of the test substance treated tissues after a 10-minute exposure period was 85%.

CONCLUSION: The notified chemical was considered to be non-irritating to the eyes.

TEST FACILITY: Harlan (2010k)

B.6. Irritation – eye

TEST SUBSTANCE: Notified chemical

METHOD

Rabbit Enucleation Eye Test (REET; study conducted in place of the OECD TG 405 Acute Eye Irritation/Corrosion test).

Observation Period: 4 hours

Remarks - Method: Five enucleated rabbit eyes were excised and allowed to equilibrate for 30 mins in a perspex clamp placed within a superfusion chamber. Saline solution was allowed to irrigate the surface of the cornea via a saline drip in the rear of the chamber. The eyes were re-examined after approximately 30 mins of equilibration to ensure that they had not been damaged during the excision. Corneal thickness was measured using an ultrasonic pachymeter. Any eyes with corneal swelling greater than 10% of the pre-enucleation measurement or stained with fluorescein were discarded.

Following inspection, 3 eyes held by perspex clamps were removed from the superfusion chamber and placed horizontally into a petri dish. 0.1 mL of the test substance was applied evenly to the surface of each of the cornea. After 10 seconds the test substance was rinsed off using a minimum 20 mL of saline solution. The remaining 2 eyes remained untreated (i.e. saline solution only) and served as negative controls.

The thickness of the cornea was measured using an ultrasonic pachymeter under a slit-lamp biomicroscope pre-enucleation, post-equilibration and at 1, 2, 3 and 4 hours following treatment. For each enucleated eye a measurement was made at the optical centre, and at four other locations at the apex of the cornea. A mean value for corneal thickness was calculated based on these four measurements. The corneal thickness for each eye 1, 2, 3 and 4 hours following treatment was used to calculate the percentage change compared with the corneal thickness pre-treatment.

The condition of the cornel epithelium was assessed (using a slit-lamp biomicroscope) at 1, 2, 3 and 4 hours following treatment. The uptake of fluorescein by the corneal epithelium was assessed pre-enucleation, post-equilibration and approximately 4 hours following treatment using a cobalt blue filter of the split-lamp biomicroscope after application of Fluorescein Sodium drops.

RESULTS

Remarks - Results: Corneal opacity was noted in all treated eyes (corneal cloudiness x area scores ≤4; control values 0).

Mean corneal swelling increased 21-76.8% in the test substance treated eyes 1-4 hours post-treatment (control values ≤9.9%).

Sloughing was observed in 2/3 test substance treated eyes from 2-4 hours following treatment (no observations in control eyes).

Slight-moderate fluorescein staining covering up to 100% of the area of the cornea was observed in test-substance treated eyes 4 hours post-treatment (fluorescein uptake scores ≤8; control values 0).

Positive control data from in-house validation of the test protocol were provided in the study report.

The results of the test indicated the potential for severe eye irritation. Accordingly, the *in vivo* eye irritation test was considered unnecessary and was not performed in the interests of animal welfare.

CONCLUSION

The notified chemical is severely irritating to the eye.

TEST FACILITY Harlan (2010f)

B.7. 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)
Remarks - Method A preliminary study was conducted at 100% concentration using one mouse. No clinical signs of toxicity were reported

A concurrent positive control study was not run, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde (HCA) (85%).

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1716.59	1.00
25	4574.71	2.66
50	4578.36	2.67
100	10676.47	6.22*

Remarks - Results No signs of systemic toxicity were noted.

The stimulation index at 100% concentration was >3, indicating a positive response. Based on these results, the EC_3 value was calculated to be 54.6%.

CONCLUSION The notified chemical was considered to be a skin sensitiser under the conditions of the test.

TEST FACILITY Harlan (2010h)

B.8. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain Rat/Wister [Crl:WI(WU)]
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 No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	6M + 6F	0	0/12
low dose	6M + 6F	75	0/12
mid dose	6M + 6F	150	0/12
high dose	6M + 6F	300	0/12
control recovery	6M + 6F	0	0/12

high dose recovery	6M + 6F	300	0/12

Clinical Observations

There were no overt clinical signs of toxicity noted for animals treated at up to 300 mg/kg bw/day. Short term reduction in activity levels was observed in animals treated at the medium dose level, however, this was not dose dependent. Statistically significant increases in water consumption were noted in animals of both sexes treated with 300 mg/kg bw/day. There were no effects on body weight or food consumption at any treatment level.

Laboratory Findings – Clinical Chemistry, Haematology and Urinalysis

Red blood cells, haemoglobin and haematocrit were statistically significantly decreased in males (low, mid and high groups) when compared to controls following the treatment period. However, the study authors report that these levels were still in the normal range for the species and strain of rat. There were no significant differences in these parameters following recovery. There were some sporadic statistically significant changes in multiple measured parameters, which the study authors suggest are unlikely to be treatment related due to the lack of a dose response.

Effects in Organs

There were no treatment related macroscopic findings in any organ at necropsy. The mean absolute and relative liver weights were statistically significantly increased in males and females in the 300 mg/kg bw/day groups after the treatment period. There were also statistically significant dose dependent increases in kidney weights in males and females in the 300 mg/kg bw/day group after treatment. These findings for liver returned to normal by the recovery period but kidney weights remained elevated. Based on recovery and/or the lack of associated histopathological effects, these findings were not considered by the study authors to be adverse.
There were also statistically significant increases in male spleen weights (300 mg/kg bw/day) after the recovery period, However, these effects were considered by the study authors to be incidental due to a lack of a treatment related response and/or associated histopathological findings.

Gastro-intestinal tract lesions were noted in males (2/6) treated at 300 mg/kg bw/day. In one male, severe acute submucosal oedema of the forestomach, focal inflammatory cell infiltration and reactive squamous cell hyperplasia were noted (1/6) in addition to focal moderate chronic inflammation in the tunica muscularis being detected. In a second male, severe focal ulceration of the rectum was noted. After the recovery period, inflammatory cell infiltrates were still detected in one male, indicating chronic ulceration. These effects were attributed by the study authors to the notified chemical.

There were numerous other sporadic histopathological findings, however, these were not considered by the study authors to be of relevance due to a lack of dose response or other specific explanations (e.g - retrobulbar haemorrhages due to blood sampling procedure).

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 150 mg/kg bw/day, based on adverse effects at 300mg/kg bw/day.

TEST FACILITY Fraunhofer (ITEM) (2010)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation and pre-incubation procedure.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *Escherichia coli*: WP2uvrA$^-$
Metabolic Activation	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Test 1	a) With metabolic activation: 5, 15, 50, 150, 500, 1500 and 5000 µg/plate b) Without metabolic activation: 5, 15, 50, 150, 500, 1500 and 5000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	A preliminary toxicity test (0-5000 µg/plate) was performed to determine the toxicity of the test material (TA100 and WP2uvrA$^-$ only).

Tests 1(plate incorporated) and 2(pre-incubated) were conducted on separate days using fresh cultures and test substance solutions. The concentration range was amended in Test 2 (0.5-500µg/plate)

Vehicle and positive controls were used in parallel with the test material. Positive controls: i) without S9: N-ethyl-N'-nitro-N-nitrosoguanidine (WP2uvrA$^-$, TA100, TA1535), 9-aminoacridine (TA1537) and 4-nitroquinoline-1-oxide (TA98); ii) with S9: 2-aminoanthracene (TA100, TA1535, TA1537, WP2uvrA$^-$) and benzo(a)pyrene (TA98).

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥500	≥500	≥1500	Negative
Test 2		≥150	>500	Negative
Present				
Test 1	≥500	≥500	≥1500	Negative
Test 2		≥500	>500	Negative

Remarks - Results

Significant increases in the frequency of revertant colonies were not recorded, with or without metabolic activation.

The test substance caused a visible reduction in the growth of the bacterial background lawn, with and without metabolic activation.

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

CONCLUSION

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

TEST FACILITY

Harlan (2009b)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain

Human

Cell Type/Cell Line

Lymphocytes

Metabolic Activation

S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver

Vehicle

Dimethyl sulphoxide

Remarks - Method

A preliminary toxicity study was performed (4 hr exposure, with and without activation and 24hr exposure without activation) at concentrations 6.48-1660 µg/mL. Haemolysis was noted at ≥51.88 µg/mL.

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

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	3.25, 6.5*, 13*, 26*, 52, 78	4 h	24 h
Test 2	3.25, 6.5*, 13*, 26*, 39*, 52	24 h	24h
Present			
Test 1	13, 26*, 52*, 78*, 104, 208	4 h	24 h

Test 2	13, 26*, 39*, 52*, 65*, 78	4 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥51.88	≥26	>78	Negative
Test 2	≥51.88	≥39	>52	Negative
Present				
Test 1	≥103.75	≥78	>208	Negative
Test 2		≥65	>78	Negative

Remarks - Results

No toxicologically significant increases in the number of cells with aberrations were noted, with or without metabolic activation. There was a modest statistically significant increase noted at 26 g/ml in the absence of metabolic activation but since this effect was not seen at the next dose level, it was considered by the study authors to have no toxicological significance.

The positive and vehicle controls gave satisfactory responses confirming 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 (2010g)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability – Study 1

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Aerobically activated sludge from domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	Biological Oxygen Demand (BOD)
Remarks - Method	No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	<1	5	69
7	<1	7	80
14	<1	14	89
21	<1	21	95
28	<1	28	99

Remarks - Results	All validity criteria for the test were satisfied. The results tabulated above are based on BOD. There was no net oxygen consumption in the abiotic control. Based on the results from the toxicity control (31% degradation by day 14) the test substance had no apparent toxic or inhibitory effect on the inoculum. The notified chemical did not pass the criterion for ready biodegradability of >60% degradation (ThOD) reached within the 10 day window.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Firmenich (2011c)

C.1.2. Ready biodegradability – Study 2

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	Activated sludge filtrate
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	Dissolved oxygen
Remarks - Method	The temperature range over the test period was 16.8 – 24.4 °C, which exceeded the guideline value of 20 – 24 °C. However, this did not affect the degradation of the reference substance and the test is therefore considered reliable. No other deviations to the protocol were reported.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	1.6	7	74.4
18	7.0	14	76.6
21	12.2	21	-
28	11.4	28	-

Remarks - Results	All validity criteria were satisfied. The degradation in the toxicity control was 31.4% by day 14 indicating the test substance is not inhibitory to biodegradation. The notified chemical did not pass the criterion for ready biodegradability of >60% degradation (ThOD) reached within the 10 day window.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Guangdong Detection Center of Microbiology (2011)

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 EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish – Semi static
Species	Zebra fish *(Brachydanio rerio)*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	125 mg $CaCO_3$/L
Analytical Monitoring	HPLC / UV-Vis
Remarks – Method	Following a limit test, a definitive test was conducted in accordance with the guidelines above with daily renewal of test medium. Since the test substance is volatile the test was performed in a closed system. One Erlenmeyer flask was used per treatment and each flask was nearly completely filled to keep the air space as small as possible. The test substance was mixed into test water (loading rate 100 mg/L) with intense stirring for 3 hours at room temperature in the dark. After stirring, the test item was left to settle for 30 minutes and the middle phase filtered through a 0.45 µm filter. The negative pressure of the filtration unit was reduced as far as possible to avoid losses of volatile components of the test item during filtration. The filtrate was used as a stock solution to prepare all test media, which were prepared just before introduction of the fish before each test medium renewal. All test media appeared as clear solutions throughout the test duration. The 96 h LC50 was calculated by probit analysis.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Mean measured**		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	-	7	0	0	0	0	0
0.45	n.a.	7	0	0	0	0	0
1.00	n.a.	7	0	0	0	0	0
2.17	1.4	7	0	0	0	0	0
4.55	3.1	7	0	0	0	1	1
10.0	5.3	7	0 †	7	-	-	-

*Determined from duplicate samples from freshly prepared and aged media at the start and end of each test medium renewal period.
n.a. = not analysed. †7 fish were tumbling during swimming.

LC50	3.1 mg/L at 96 hours (based on mean measured concentrations) 95% CI 2.4 – 4.2 mg/L
NOEC	1.4 mg/L at 96 hours (based on mean measured concentrations)
Remarks – Results	All validity criteria were satisfied and no significant deviations to the protocol were reported. The measured concentration varied from 53-64%

of the nominal concentration, therefore, the reported results are based on the measured concentration. Although there were no mortalities after 3 hours at test concentration 5.3 mg/L, all the fish exhibited sub-lethal effects, i.e. tumbling during swimming.

CONCLUSION The notified chemical is toxic to fish

TEST FACILITY Harlan (2011a)

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 – Static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC UV-Vis
Remarks - Method	Following a range-finding test, a definitive test was conducted in accordance with the guidelines above. As the test substance is volatile the test was performed in a closed system. One Erlenmeyer flask was used per treatment and each flask was nearly completely filled to keep the air space as small as possible. The test substance was mixed into test water (loading rate 100 mg/L) with intense stirring for 3 hours at room temperature in the dark. After stirring, the test item was left to settle for 30 minutes and the middle phase filtered through a 0.45 µm filter. The negative pressure of the filtration unit was reduced as far as possible to avoid losses of volatile components of the test item during filtration. The filtrate was used as a stock solution to prepare all test media, which were prepared just before the start of the test. All test media appeared as clear solutions throughout the test duration. The NOEC, EC0 and EC100 were determined directly from the raw data. The 48 h EC50 was determined from the geometric mean of the EC0 and EC100.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Mean measured**		*24 h*	*48 h*
Control	-	20	0	0
0.3125	n.a.	20	0	0
1.00	n.a.	20	0	0
3.125	1.4	20	0	0
10.0	4.5	20	19	20
31.25	17	20	20	-
100	56	20	-	-

*Measured on duplicate samples taken from each treatment before the test start and at the end of the test after 48 hours.
n.a. = not analysed

EC50	2.5 mg/L at 48 hours (based on mean measured concentrations) 95% CI reported as 1.4 – 4.5 mg/L
NOEC	1.4 mg/L at 48 hours (based on mean measured concentrations)
Remarks - Results	All validity criteria were satisfied and no significant deviations to protocol were reported. The measured concentration varied from 45-56% of the nominal concentration, therefore, the reported results are based on the measured concentration.

CONCLUSION The notified chemical is toxic to daphnia.

TEST FACILITY Harlan (2011b)

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: Control, 0.32, 1.00, 3.13, 10.0, 31.3 and 100 mg/L
Mean measured concentrations: Control, 0.18, 0.32, 0.86, 2.0, 23 and 82 mg/L (calculated as the geometric means of the concentrations measured at the start and the end of the study)
Auxiliary Solvent None
Water Hardness 0.24 mM Mg^{2+} and Ca^{2+}
Analytical Monitoring HPLC UV-Vis
Remarks - Method Following a range finding test, a definitive test was conducted according to the guidelines above. The test substance was mixed into test water (loading rate 100 mg/L) with intense stirring for 3 hours at room temperature in the dark. After stirring, the test item was left to settle for 30 minutes and the middle phase filtered through a 0.45 µm filter. The negative pressure of the filtration unit was reduced as far as possible to avoid losses of volatile components of the test item during filtration. The filtrate was used as a stock solution to prepare the lower test concentrations. As the test substance is volatile the test was performed in a closed system. Erlenmeyer flasks were completely filled and made tight with glass stoppers to avoid loss of test substance. The 72 hour EC50 was determined by Probit analysis. The NOEC was determined by average growth rate and yield were compared to control values by Welch t-tests and Williams test. A positive control test was performed by exposing algae to potassium dichromate to evaluate algal quality and experimental conditions.

RESULTS

Biomass		*Growth*	
E_yC50 mg/L at 72 h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
1.3	0.18	3.8	0.18
95% CI 1.1 – 1.4 mg/L		95% CI 3.3 – 4.7 mg/L	

Remarks - Results All validity criteria were satisfied and no significant deviations to the protocol were reported. The mean measured test substance concentrations were determined as the geometric means of the concentrations measured at the start and the end of the study. The mean measured concentrations varied from 20-82% of the nominal concentration at the beginning of the test and the measured concentration decreased to below the limit of quantification (LOQ = 0.234 mg/L) for the 0.32 and 1.0 mg/L test solutions. The 72 h EC50 for the positive control test was 0.94 mg/L based on growth rate which was within the normal range for the reference material.

CONCLUSION The notified chemical is toxic to algae

TEST FACILITY Harlan (2011c)

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 sewage sludge from domestic sewage treatment plant
Exposure Period	3 hours
Concentration Range	Nominal: 10, 32, 100, 320, 1000 mg/L Actual: Not measured
Remarks – Method	A definitive test was conducted according to the guidelines above at test substance concentrations of 10 – 1000 mg/L. At each test concentration, the test material was dispersed in water and subjected to 15 min ultrasonication followed by 24 hours of mixing. The test vessels were shielded from light during mixing. A blank control and reference (3,5-dichlorophenol) control were run in parallel. The rate of respiration was determined after 3 hours contact time and compared to the results from the control and reference material. Test conditions: 21 ± 1 °C, pH 7.5 – 7.9.
RESULTS	
IC50	150 mg/L at 3 hours (95% CI 130 – 180 mg/L)
NOEC	57 mg/L
Remarks – Results	All validity criteria were satisfied and no significant deviations to protocol were reported.
CONCLUSION	The notified chemical is not expected to be inhibitory to micro-organisms at concentrations <150 mg/L
TEST FACILITY	Harlan (2010i)

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