File No: LTD/1785

November 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Yasminate

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

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1785	Firmenich Limited	Yasminate	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 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*
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:

R43 May cause sensitisation by skin contact

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 at ≤ 0.1% in cosmetic products, and ≤ 0.5% 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 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:
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

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

- 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 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

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 0.1% in cosmetic products and ≤ 0.5% in household products.

Disposal

- Where reuse or recycling are not available or practical, dispose of the 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 0.1% in cosmetic products or 0.5% in household products;
- information becomes available on the repeated dose toxicity potential of the notified chemical;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- 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, impurities and additives/adjuvants.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: adsorption/desorption, dissociation constant, flammability limits, explosive and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
USA (2004), EU (2004), Philippines (2007), Switzerland (2007)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Yasminate

MOLECULAR WEIGHT
< 500 Da

ANALYTICAL DATA
Reference GC, NMR, UV, IR and GC-MS 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 ± 0.5 °C	Measured
Boiling Point	Decomposed at ~ 182 °C, prior to boiling, at 97.5 kPa	Measured
Density	1051 kg/m^3 at 20 ± 0.5 °C	Measured
Vapour Pressure	8.7 x 10^{-4} kPa at 25 °C	Measured
Water Solubility	5.26 x 10^{-4} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ = 16.5, 17.0, and 13.6 days at 40 °C and pH 5, 7, and 8.5	Measured
Partition Coefficient (n-octanol/water)	log Pow ≥ 5.6	Measured
Adsorption/Desorption	Log K_{OC} = 4.1	Calculated using KOCWIN v 2.00 (US EPA, 2011)
Dissociation Constant	Not determined	The notified chemical is expected to be

		ionised in the environment due to the presence of a dissociable group.
Flash Point	159 ± 2.0 °C at 101.3 kPa	Measured
Autoignition Temperature	> 220 °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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia at 100% concentration, as well as a component of compounded fragrance formulations (at concentrations ≤ 5%) and various formulated end-use cosmetic and household products (at concentrations ≤ 0.5%).

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 Limited

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 100% concentration) will be imported into Australia in lacquered drums of sizes ranging from 5 kg up to 180 kg. The end-use products (≤ 0.5% notified chemical) will be packaged in typical consumer-sized containers suitable for retail sale.

The notified chemical will be transported from the port of entry by road to the notifier's warehouse facilities for storage in its original packaging until transportation to the customer site. Alternatively, the notified chemical and products containing it will be shipped directly from the port of entry to the customer site.

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic (≤ 0.1% concentration) and household (≤ 0.5% concentration) products.

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

At the customer facilities, the procedures for incorporating the imported fragrance preparations (containing ≤ 100% notified chemical) into end-use products will likely vary depending on the nature of the cosmetic and 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.

Household products
Household products containing the notified chemical at ≤ 0.5% concentration may be used by consumers and professional workers. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines, or open processes and manually applied by rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 0.1% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	unknown	unknown
Mixer	4	2
Drum Handling	4	2
Drum Cleaning/washing	4	2
Maintenance	4	2
Quality Control worker	0.5	1
Packager	4	2
End users (professionals)	unspecified	unspecified

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical, at 100% concentration or as a component of the imported fragrance preparations (≤ 5% concentration) or end-use products (≤ 0.5% concentration), only in the event of accidental rupture of containers.

At the notifier facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing the notified chemical at ≤ 100% concentration. Exposures of these workers will be limited to situations of an accidental discharge, spill or leaking drum, requiring clean up. If such an event occurs, a worker may be exposed through dermal or ocular contact. The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective clothing, chemical resistant gloves, and eye protection.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection, impervious gloves and respiratory protection (if appropriate).

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤ 0.1% concentration) to clients (e.g. hair dressers, workers in beauty salons) or the use of household products (at ≤ 0.5% concentration) in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may

use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or 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 through the use of the household products and the leave-on and rinse-off cosmetics (≤ 0.1 – 0.5% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

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
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – Buehler non-adjuvant test.	inadequate evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (10%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Rat, phototoxicity	no evidence of phototoxicity

Toxicokinetics, metabolism and distribution.
No toxicokinetic data were provided on the notified chemical. Based on the water solubility (5.26×10^{-4} g/L at 20 °C), partition coefficient (log $K_{ow} \geq 5.6$) 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 (although the extent of absorption may be limited). The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
The notified chemical was found to have low acute toxicity by the oral route in a study conducted in rats.

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

Irritation
In an acute dermal irritation study in rabbits, a single 4-hour, semi-occluded application of the notified chemical resulted in well-defined erythema at all treated sites 1 hour after patch removal, and at the 24 and 48 hour observations. By the 72 hour observation, erythema had decreased to very slight. Very slight to slight oedema was also seen in all animals in that time period. Severe desquamation was noted at all treated sites at the 7 day observation, but by day 14 all treated sites appeared normal.

In a rabbit eye irritation study, minimal to moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment, with only minimal conjunctival irritation evident in one treated eye at the 24 hour observation.

The effects observed in these studies did not warrant classification of the chemical as a skin or eye irritant.

Sensitisation.
The potential for skin sensitisation to be induced by the notified chemical was assessed in a Buehler Test in guinea pigs (19 animals; 100% induction concentration). At challenge (at 100% concentration), positive responses were evident in 2 and 1 animals 24 and 48 hours after patch removal, respectively. At rechallenge (at 75% concentration) positive responses were evident in 3/19 animals 24 hours after patch removal, with no skin responses evident after 48 hours. Neither of the 2 test animals that showed positive responses at challenge was considered to have shown a positive response at rechallenge. Based on the results of the study (and on the evaluation system used), the study authors did not consider the notified chemical to be skin sensitiser.

The notified chemical was subsequently tested in an LLNA study in mice (tested at 1, 5, 10, 20 and 40% concentration, with 20 and 40% producing stimulation indices of 10.4 and 19.5, respectively) and found to be a skin sensitiser. The EC_3 value was calculated to be 6.03%.

In a human repeat insult patch test (HRIPT) completed on 102 subjects, the notified chemical (at 10% concentration) was not considered by the study authors to induce skin sensitisation. A minimal or doubtful response (presented with slightly different surrounding skin) was noted in 1 subject 24 hours post challenge patch removal; however, no reaction was evident at the 48 hour observation.

Repeated dose toxicity.
No repeated dose toxicity data were provided for the notified chemical.

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

Phototoxicity.
In a human phototoxicity patch test completed on 21 subjects, there was no evidence of phototoxicity to the notified chemical.

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 following table.

Hazard classification	***Hazard statement***
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(s):

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 ≤ 100% concentration) may occur during blending operations. The notified chemical has the potential to cause slight skin irritation and is considered to be a skin sensitiser. In addition, harmful effects following repeated exposure and/or 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 ≤ 0.5% 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

Irritation
Skin and eye irritation effects are not expected from use of the notified chemical at the proposed concentrations in cosmetic and household products.

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 fragrances (containing 0.1% 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 3.75 µg/cm^2 (Cadby *et al.*, 2002). Following consideration of the available data on skin sensitisation (and the study details/results of these studies) and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 15.84 µg/cm^2 was derived (using the EC3 value of 6.03%, which was obtained in the LLNA study on the notified chemical). In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of ~100.

As the AEL>CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical in fine fragrances (a worst case example of a cosmetic product) at ≤ 0.1% concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level from other cosmetic (containing ≤ 0.1% notified chemical) and household products (containing ≤ 0.5% 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.

Repeat dose toxicity
The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low concentration of the notified chemical in end use products.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.1% concentration in cosmetic products and ≤ 0.5% in household products, is not considered to be unreasonable. In the absence of data on the repeated dose toxicity potential of the notified chemical, use of the notified chemical is supported only under limited exposure conditions, which are reflected in the low concentration of the notified chemical in end-use products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported into Australia at 100% concentration or in the form of fragrance preparations for further reformulation into end-use cosmetic and household products. Environmental release of the notified chemical during transportation and storage will be limited to accidental spills or leaks of drums, which is expected to be minimal.

A typical blending operation will be highly automated in a fully enclosed/contained environment. Potential sources of release include spills, equipment washing, and container residues. A total of 0.1% of waste may be generated as a result of spills. It is expected that this equipment will be cleaned using water that will be reused for the subsequent operations. The average amount of residue in empty containers after removal by vacuum pump is estimated to be < 0.1%. Therefore a total of 0.2% of waste will be generated each year from reformulation processes.

RELEASE OF CHEMICAL FROM USE
The notified chemical will enter the aquatic compartment during use of the various end-use products into which it will be incorporated. It is estimated that a maximum of 3% of the consumer products may remain in the consumer containers once the consumer products are used up.

RELEASE OF CHEMICAL FROM DISPOSAL
Empty containers containing the notified chemical at blending facilities will be recycled or disposed of through an approved waste management facility. Empty product containers are expected to be disposed of to landfill.

7.1.2. Environmental Fate

The notified chemical is not readily biodegradable based on the provided test report. However, it is considered to have inherent, primary biodegradability. For the details of the environmental fate studies please refer to Appendix C. It is expected to have bioaccumulative potential based on the reported log P_{OW} of > 5.6. This is not considered to be a concern since the notified chemical showed a biodegradability of 58% in 28 days. The notified chemical is also expected to be ionised in the environment due to the presence of an acidic group. The presence of ionic functional groups suggests a low bioaccumulation potential (Schuurmann, et al., 1995). A BCF of < 2000 was also predicted using BCFBAF v3.01 (US EPA, 2011). The half-life of the notified chemical in air is calculated to be 1.26 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.

Most of the notified chemical will be released to the sewer after use and directed to sewage treatment plants (STPs) nationwide. A small amount of the notified chemical may be sent to landfill as collected spills or container residues. In STPs, the majority of the notified chemical is expected to be removed from the water column via adsorption to sludge sediment given the hydrophobic structure and the estimated logK_{OC} of 4.1, and eventually be sent to landfill. In landfill or water, the notified chemical is expected to undergo biotic or abiotic degradation processes, forming water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated assuming a worst case scenario of 100% release of the notified chemical into sewer systems nationwide and no removal from 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	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:	0.06	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 notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted. By using ECOSAR (US EPA, 2011), the following acute toxicity data have been predicted for the notified chemical.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 0.12 mg/L	Very toxic to fish
Daphnia Toxicity	48 h EC50 = 0.15 mg/L	Very toxic to *Daphnia*
Algal Toxicity	72 h EC50 = 0.49 mg/L	Very toxic to alga

The notified chemical is considered to be very toxic based on the above predicted endpoints. These data are for risk assessment purposes only. Modelled data are not used for the Globally Harmonised System of Classification

and Labelling of Chemicals (GHS; United Nations, 2009). Therefore, the notified chemical has not been formally classified under GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) was calculated using the predicted endpoint for fish which is considered to be the most sensitive species. A conservative safety factor of 100 was used as acute toxicity values from three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Fish)	0.12	mg/L
Assessment Factor	100	
PNEC:	1.20	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.61	1.2	0.51
Q - Ocean:	0.06	1.2	0.05

The risk quotient (RQ = PEC/PNEC) 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. Therefore, on the basis of the PEC/PNEC ratio and the assessed use pattern, 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.
Remarks The test material remained unchanged in appearance during cooling (using a dry ice/isopropanol bath).
Test Facility Firmenich (2003)

Boiling Point Decomposed at ~ 182 ± 0.5 °C, prior to boiling, at 97.5 kPa

Method OECD TG 103 Boiling Point.
Remarks Determined according to the Siwoloboff method.
As the test material decomposed during testing, additional work was attempted by Differential Scanning Calorimetry (DSC), which indicated that decomposition of the test material started at 160 °C.
Test Facility Firmenich (2003)

Density 1051 kg/m^3 at 20.0 ± 0.5 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Determined using the Oscillating density meter method.
Test Facility Firmenich (2003)

Vapour Pressure 8.7 x 10^{-4} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
Remarks Determined using the dynamic measurement method.
Test Facility Firmenich (2005a)

Water Solubility 5.26 x 10^{-4} g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method. Five mixtures of the notified chemical with distilled water at 10-13 mg/L were shaken at approximately 30 °C for 24 to 120 hours. After standing at 20 °C for a period of not less than 24 hours, the mixtures were centrifuged at 10000 rpm for 20 minutes. The concentration of the sample solutions was determined by gas chromatography and was averaged to be 5.26 x 10^{-4} g/L at 20 °C
Test Facility SafePharm (2003)

Hydrolysis as a Function of pH $t_{½}$ = 16.5, 17.0, and 13.6 days at 40°C and pH 5, 7, and 8.5, respectively

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

pH	*T (°C)*	*$t_{½}$ (days)*
2	40	17.3
5	40	16.5
7	40	17.0
8.5	40	13.6

Remarks The disappearance of the notified chemical after 5 days was between 10 and 20% at pH 2, 5, 7 and 8.5 at 40 °C.The determined half-life at different pH indicates that the notified chemical is less stable under basic conditions. The half-life at 40 °C was less than 1 day at pH 12.
Test Facility Firmenich (2014)

Partition Coefficient (n-octanol/water) log Pow ≥ 5.6

Method	OECD TG 117 Partition Coefficient (n-octanol/water)..
Remarks	HPLC Method. The partition coefficient of the notified chemical has been determined to be ≥ 5.6.
Test Facility	SafePharm (2003)

Flash Point 159 ± 2 °C at 101.3 kPa

Method	Commission Directive 92/69/EEC A.9 Flash Point.
Remarks	Determined using a closed cup equilibrium method.
Test Facility	Firmenich (2003)

Autoignition Temperature > 220 °C

Method	Determined using the Firmenich FIRELAB instrument.
Remarks	Analysis conducted using the notified chemical in crude form.
Test Facility	Firmenich (2005b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/ Sprague-Dawley (Crl: CD (SD) IGS BR)
- Vehicle: None.
- Remarks - Method: No significant protocol deviations. GLP Compliance.

RESULTS

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

- LD50: > 2,000 mg/kg bw.
- Signs of Toxicity: There were no clinical effects or signs of systemic toxicity noted in any of the animals over the study period.
- Effects in Organs: No abnormalities were noted at necropsy.
- Remarks - Results: All animals survived until the scheduled termination and showed gains in bodyweight over the study period.

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

TEST FACILITY: Safepharm (2003b)

B.2. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 3M
- Vehicle: None.
- Observation Period: 14 days.
- Type of Dressing: Semi-occlusive.
- Remarks - Method: No significant protocol deviations. GLP Compliance.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1.67	1.67	1.67	2	< 7 days	0
Oedema	1.67	1	1	2	< 7 days	0

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

- Remarks - Results: Well defined erythema was noted at all treated sites 1 hour after patch removal, and at the 24 and 48 hour observations. By the 72 hour observation, erythema had decreased to very slight.

  Slight oedema was noted at all treated sites 1 hour after patch removal and at the 24 hour observation, decreasing to very slight oedema at the 48 hour or 72 hour observation.

Severe desquamation was noted at all treated skin sites at the 7 day observation. All treated skin sites appeared normal at the 14 day observation.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY Safepharm (2003c)

B.3. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3M
Observation Period 72 hours.
Remarks - Method No significant protocol deviations.
GLP Compliance.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0	0.3	2	< 48 hours	0
Conjunctiva: chemosis	0	0	0	1	< 24 hours	0
Conjunctiva: discharge	0	0	0	1	< 24 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results Minimal to moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment, with only minimal conjunctival irritation evident in one treated eye at the 24 hour observation.

No corneal opacity or iridial inflammation was observed at any of the measuring intervals.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Safepharm (2003d)

B.4. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation - Buehler test.
Species/Strain Guinea pig/Hartley albino.
PRELIMINARY STUDY Maximum minimally irritating Concentration:
topical: 100%
MAIN STUDY
Number of Animals Test Group: 20 (9F & 11M) Control Group: 20F (10 each for the challenge & rechallenge phases)
INDUCTION PHASE Induction Concentration:
topical: 100%
Signs of Irritation Very faint erythema was observed on the application site of all animals treated with the test substance, on various days throughout the three weeks of administration.
CHALLENGE PHASE

1st challenge	topical: 100%
2nd challenge	topical: 75%
Remarks - Method	The test substance was used neat or prepared in mineral oil. A preliminary test was conducted at 25-100% concentration (using 4 animals) to determine the appropriate concentrations for use in the induction and challenge phases. The induction phase consisted of 9 applications over 3 weeks. No positive control test was run in parallel to the main test, however it had been conducted previously in the test laboratory using α-Hexylcinnamaldehyde.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group					
challenge	100%	2/19	1/19	-	-
rechallenge	75%	-	-	3/19	0/19
Naïve Control Group					
challenge	100%	1/10	0/10	-	-
rechallenge	75%	-	-	0/10	0/10

Remarks - Results

During the induction phase, one female animal was euthanized prior to the 24 hour observation of the second induction. This animal had been found housed with a male animal and the study authors could not rule out pregnancy, hence the animal was humanely terminated. The remaining 19 test animals survived and gained weight over the entirety of the study period.

Very faint erythema was not considered a positive skin reaction by the study authors (only animals showing a greater response are reflected in the above table).

In the first challenge phase, very faint to faint erythema was noted at 18/19 test sites after the challenge application. This degree of irritation persisted at 6 test sites through to the 48 hour observation (very faint to faint erythema was also noted at the test sites of 7/10 control animals at the 24 and/or 48 hour observations).

In the second challenge phase, very faint to faint erythema was noted at sixteen of the nineteen test sites after the challenge application. This degree of irritation persisted at eleven test sites through to the 48 hour observation (very faint to faint erythema was also noted at the test sites of 3/10 control animals at the 24 and/or 48 hour observations)..

Neither of the 2 test animals that showed positive responses in the 1st challenge phase was considered to have shown a positive response in the 2nd phase.

For the test substance to be considered by the study authors as a potential contact sensitiser, positive responses were required in ≥ 15% of the test animals (in the absence of similar responses in the control animals) and a positive reaction was required to persist to 48 hours in ≥ 1 animal.

CONCLUSION

There was inadequate evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY PSL (2004)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/ CBA/J
Vehicle Acetone/olive oil (AOO; 4:1)
Positive Control Isoeugenol (in AOO)
Remarks - Method No significant protocol deviations.
GLP Compliance.

The study was repeated (repeat study results discussed below), as the initial study results, particular with respect to the positive control, indicated an apparent increased sensitivity of the assay (higher than expected stimulation indices obtained).

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	32.1	-
1%	35.3	1.1
5%	51.3	1.6
10%	92.9	2.9
20%	334.6	10.4
40%	626.9	19.5
Positive Control		
0.5%	37.2	1.2
1.0%	102.3	3.2
5.0%	278.4	8.7

Remarks - Results No signs of irritation or systemic toxicity were noted in the test or control animals.

An EC-3 (linear model) of 1.3% was calculated for the positive control. An EC-3 (linear model) of 6.03% was calculated for the notified chemical.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY BRT (2003)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (10% concentration in DEP)

METHOD Repeated insult patch test with challenge
Study Design Induction Procedure: patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday).
Rest Period: 10-15 days
Challenge Procedure: a patch was applied to a naïve site. Patches were removed by the applicants after 24 hours. Sites were graded 24 and 48 hours post-patch removal.

Study Group	84 F, 31 M; age range 18 to 72 years
Vehicle	Diethyl Phthalate (DEP)
Remarks - Method	The test substance was spread on a 2 cm × 2 cm occluded patch. A pilot study (completed by 16/18 subjects, aged 20 to 75 years), using 10% notified chemical, was conducted prior to the main study. No evidence of sensitisation was noted. A panel of 115 healthy human subjects (devoid of any physical or dermatological conditions) was amassed. Of these, 102 test subjects completed the study (8 subjects were lost to follow up, 5 subjects voluntarily withdrew; 0-9 induction observations recorded).

RESULTS

Remarks - Results	One subject was noted to have a minimal or doubtful response (presented with slightly different surrounding skin) 24 hours post challenge patch removal, with no reaction evident at the 48 hour observation. No reactions were evident in any other test subject during the induction or challenge phases.

CONCLUSION The test substance was non-sensitising under the conditions of the test.

TEST FACILITY TKL (2004a)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone-induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5 - 5,000 µg/plate b) Without metabolic activation: 5 - 5,000 µg/plate
Vehicle	Dimethyl Sulphoxide (DMSO)
Remarks - Method	No significant protocol deviations. GLP Compliance. A preliminary toxicity test (0-5,000 µg/plate) was performed to determine the toxicity of the test material (using TA100 strain) in both the presence and absence of metabolic activation. No toxicity to the background lawn was evident, however, significant decreases in revertant colony frequency were noted in the presence of S9. Positive control tests were conducted in parallel to the main test using N-ethyl-N'-nitro-N-nitrosoguanidine (TA100 and TA1535), 9-aminoacridine (TA1537), Mitomycin C (TA102) and 4-nitroquinoline 1-oxide (TA98). In addition, 2-Aminoanthracene (TA100, TA1535 and TA1537), Benzo(a)pyrene (TA98) and 1,8-Dihydroxyanthraquinone (TA102), were also used as positive controls in the presence of S9 mix

RESULTS

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

Present				
Test 1	> 5,000	> 5,000	≥ 1,500	negative
Test 2		> 5,000	≥ 1,500	negative

Remarks - Results

Similar to the preliminary toxicity test, the study authors considered that the test material exhibited no toxicity to the bacterial background lawns. However, significant decreases in revertant colony frequency were noted in the presence of metabolic activation (from 500 µg/plate).

In Test 1, a small statistically significant increase in revertant colony frequency was observed in tester strains TA100 (with S9 mix) and TA102 (without S9 mix) at 150 and 50 µg/plate, respectively. Since these increases were not reproduced in Test 2, lacked a discernible dose-response relationship and were only ~1.2 times the vehicle control values, they were considered by the study authors to be of no biological relevance.

The positive controls produced satisfactory responses, thus 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

Safepharm (2003e)

B.8. Phototoxicity – human volunteers

TEST SUBSTANCE

Notified chemical

METHOD

Phototoxicity patch test response in human subjects

Study Design

The test substance (neat) was evaluated in parallel with 4 other substances

Preparatory procedure: The test subjects had 6 equal sized skin areas irradiated for varying exposure times (increased at each site by a factor of 1.25). Irradiation was conducted with full spectrum UVL (UVB plus UVA) and evaluation was undertaken 16 to 26 hours later to determine the Minimal Erythemal Dose (MED), indicated by the site exhibiting the least amount of perceptible erythema.

Test sites: Three equal sized areas of virgin skin on the subject's backs were selected, with 2 sites treated with the test substance. One of the treated sites was then irradiated using a filtered light source, with the other treated site serving as a non-irradiated control. The third (untreated) site served as the irradiated control.

Light source: A Xenon Arc Solar Simulator (150 W) was used to emit in the UVA (320 – 400 nm) and UVB (290 – 320 nm) range. A
UVB-absorbing filter was then used to eliminate erythemogenic wavelengths below 320 nanometers, to allow delivery of only UVA irradiation.

Treatment: 0.2 mL of the test substance was applied to a 2 cm × 2 cm Webril pad on an adhesive dressing to form an occluded patch that was applied to subjects. The patches were removed after 24 hours and the appropriate sites were irradiated with 24 J/cm^2 of UVA (320 – 400 nm) irradiation. Test and control sites were examined at 24 and 48 hours after the irradiation (48 and 72 hours after the application).

Study Group

20 F, 2 M; age range 20 to 75 years

Vehicle

None

Remarks - Method

A panel of 22 healthy human subjects (devoid of any physical or dermatological conditions) was amassed. Of these, 21 (19 female and 2

male) test subjects completed the study (1 female subject was discontinued by the study authors prior to the 24 hour observation following irradiation, as the subject was deemed to have an inadequate MED).

RESULTS

Remarks - Results

No subjects showed any clinical reactions at the patch removal observation.

At the 24 hour reading following irradiation, seven subjects showed mild, but definite erythema at both irradiated sites, with an additional 2 or 1 subjects showing minimal or doubtful erythema at the treated and irradiated control sites, respectively.

Only one subject was noted to have a minimal or doubtful response at the irradiated sites 48 hours following irradiation. This response was also noted in this subject at the non-irradiated control site, at both the 24 and 48 hour observations.

Several subjects were observed to develop hyperpigmentation of both irradiated sites, at the 24 and 48 hour readings. No other clinical reactions were noted.

Six subjects did not show any reactions during the course of the study.

CONCLUSION

Under the conditions employed in this study, there was no evidence of phototoxicity to the notified chemical.

TEST FACILITY

TKL (2004b)

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. US EPA Fate, Transport, and Transformation Test Guidelines OPPTS 835.3110 Paragraph (m).
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	Not applied
Analytical Monitoring	The degradation of the test material was assessed by the determination of carbon dioxide produced.
Remarks - Method	No significant protocol deviations. GLP Compliance. The notified chemical was adsorbed onto granular silica gel prior to dispersion in the test medium to give a final test concentration of 10 mg C/L. Control tests with inoculum and the reference substance, sodium benzoate, together with a toxicity control were performed for validation purposes.

RESULTS

Test substance		*<Reference Substance>*	
Day	*% Degradation*	*Day*	*% Degradation*
2	12	1	14
14	51	10	67
28	58		

Remarks - Results	All the test validity criteria were met. The toxicity control reached 78% degradation by day 28, indicating the notified chemical was not toxic to the sludge micro-organisms. The test results in the table above indicate that the notified chemical is not readily biodegradable. The notified chemical attained 58% degradation after 28 days and failed the 10-day window. Therefore, it cannot be considered to be readily biodegradable under the strict terms and conditions of OECD Guideline No 301B. However, the test material has exhibited inherent, primary biodegradability.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Firmenich (2003)

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