File No: LTD/1575

August 2012

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Vertoxime

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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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 SUBSTANCE	INTRODUCTION VOLUME	USE
LTD/1575	Firmenich Limited	Vertoxime	Yes	<1 tonne per annum	Component of cosmetic and household products

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the data provided, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

R22 Harmful if swallowed
R38 Irritating to skin
R43 May cause sensitisation by skin contact

and

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 category	*Hazard statement*
Acute toxicity	Category 3	Toxic if swallowed Toxic in contact with skin
Skin Sensitisation	Category 1	May cause an allergic skin reaction

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the 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

- Safe Work Australia, should consider the following health hazard classification for the notified chemical:
  - Xn: R22 Harmful if swallowed
  - Xi: R38 Irritating to skin
  - Xi: R43 May cause sensitisation by skin contact

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - Conc. ≥25%: Xn; R22; R38; R43;
  - ≥20% Conc. <25%: Xi; R38; R43;

- ≥1% Conc. <20%: Xi; R43.

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

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with skin and eyes

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - 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.

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;
  - information associated with the repeated dose and/or carcinogenicity of the notified chemical becomes available;
  - the concentration of the chemical exceeds or is intended to exceed 0.002% in fine fragrances, 0.02% in other cosmetic products and 0.5% 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 MSDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with the United States Environmental Protection Agency (US EPA). Information pertaining to the assessment of the notified chemical by the US EPA was provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment, including the recommendations on safe use of the notified chemical, were carried out by NICNAS.

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, additives/adjuvants and identity/data on an analogue chemical.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: density, vapour pressure, adsorption/desorption, flammability and autoignition temperature.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Chemical (LVC) permit

NOTIFICATION IN OTHER COUNTRIES
USA (2002), Philippines (2006), Canada (2005), Switzerland (2006)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Vertoxime

MOLECULAR WEIGHT
<500 Da

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

3. COMPOSITION

DEGREE OF PURITY >90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: colourless liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	<-20 ºC	Measured
Boiling Point	192 ± 0.5 ºC at 99.97-100.17 kPa	Measured
Density	889-895 kg/m^3 at 20 ºC	Product specification sheet
Vapour Pressure	1.59 x 10^{-2} kPa at 25 ºC	Estimated - mean VP of Antoine & Grain methods (US EPA, 2009)
Water Solubility	2.54 g/L at 20 ºC	Measured
Hydrolysis as a Function of pH	≥55% (pH 2-6) and ≤35% (pH 7-12) at 40 ºC, 28 days	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.31at 20 ºC	Measured
Adsorption/Desorption	log K_{oc} = 2.00	Calculated (KOCWIN v2.00, from log Kow, USEPA, 2009).
Dissociation Constant	Not determined	Not expected to be ionised in the environmental pH range (4-9)
Flash Point	81 ± 2 ºC at 101.3 kPa (closed cup)	Measured. Classified as a C1 combustible liquid (NOHSC, 2001).
Flammability	Not determined	Based on the flash point, not classified as flammable (NTC, 2007)
Autoignition Temperature	310 ± 5 ºC	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 not assessed by the US EPA, refer to Appendix A.

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

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However, the data above do not address all Dangerous Goods endpoints. Therefore, consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

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 (≤0.5%) 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 ≤0.5% concentration) will be imported in

tightly closed lacquered drums, typically of 180 kg size, but also 100, 50, 25 10 or 5 kg. They 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 domestic products (proposed usage concentration: 0.002% concentration in fine fragrances, 0.02% in other cosmetic products and 0.5% in household products).

OPERATION DESCRIPTION
The procedures for incorporating the imported products (containing ≤0.5% 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.

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 products or end-use products (≤0.5%), only in the event of accidental rupture of containers.

During formulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤0.5% 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 such as coveralls, safety glasses and impervious gloves.

Exposure to the notified chemical in end-use products (at ≤0.5% 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 personal protective equipment 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 ≤0.5% 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 or used in hot water.

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 has been used for calculation purposes.

- Cosmetic products (Dermal exposure):

Product type	**Amount** (mg/day)	**C** (%)	**RF**	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	0.02	1	0.026
Face cream	1540	0.02	1	0.0051
Hand cream	2160	0.02	1	0.0072
Fine fragrances	750	0.002	1	0.00025
Deodorant spray	1430	0.02	1	0.005
Shampoo	10460	0.02	0.01	0.00035
Shower gel	18670	0.02	0.01	0.00062
Hand soap	20000	0.02	0.01	0.00067
Hair styling products	4000	0.02	0.1	0.0013
Total				0.046

C = concentration; RF = retention factor.
Daily systemic exposure = Amount x C(%) x RF x dermal absorption (%)/body weight (60 kg)

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

Product type	**Amount** (g/use)	**C** (%)	**Product Retained** (%)	**Percent Transfer** (%)	**Daily systemic exposure** (mg/kg bw/day)
Laundry liquid	230	0.5	0.95	10	0.018
Fabric softener	90	0.5	0.95	10	0.0071
Total					0.025

Daily systemic exposure = amount x concentration x product retained x percent transfer 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	0.5	1980	0.01	0.01	0.007	0.00017
Dishwashing liquid	3	0.5	1980	0.009	0.01	0.03	0.0013
All-purpose cleaner	1	0.5	1980	1.0	0.01	0.007	0.012
Total							0.013

Daily systemic exposure = frequency of use x concentration x body surface contact area x product concentration x film thickness on skin x time scaling 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)
Hair spray	2	10	0.02	23	15	2	0.0080

C = concentration.
Daily systemic exposure = Frequency x Amount x C(%) x Inhalation rate x Exposure duration x Airspace volume x bioavailability via the inhalation route/body weight (60 kg)

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 0.093 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 protective enough 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	LD50 between 200-2,000 mg/kg bw; harmful
Rabbit, skin irritation	irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	evidence of sensitisation
Guinea pig, skin sensitisation –non-adjuvant test.	inadequate evidence of sensitisation
Human, skin sensitisation – RIPT (1%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic

In addition, published data/information on a structurally similar analogue of the notified chemical is available and, where relevant, is briefly discussed below (the identity of the analogue chemical and information sources are considered exempt information).

Toxicokinetics, metabolism and distribution.
Based on the water solubility (2.54 g/L at 20 ºC), partition coefficient (log P_{ow} = 2.31 at 20 ºC) 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. The notified chemical may hydrolyse in the stomach to form hydroxylamine.

Acute toxicity.
The notified chemical was found to be harmful in an acute oral toxicity study in rats. All 3 animals that were treated at 2000 mg/kg bw were found dead within 24 hours of dosing, after exhibiting signs of systemic toxicity (included a comatose state, hunched posture, lethargy, ataxia, decreased respiratory rate, laboured respiration, ptosis and splayed gait). Haemorrhagic or abnormally red lungs, dark liver, dark kidneys and haemorrhagic small intestine were noted at necropsy. Signs of systemic toxicity were also noted in the animals (males only) treated at 200 mg/kg bw, however, the animals recovered within 24 hours of dosing.

Acute dermal and inhalation toxicity data were not provided for the notified chemical. A structurally similar analogue of the notified chemical is classified with the risk phrase R21: Harmful in contact with skin, therefore the potential for adverse acute effects from the notified chemical via the skin cannot be ruled out.

Irritation.
The notified chemical was determined to be irritating to the skin of rabbits, with very slight to well-defined erythema and very slight to slight oedema noted. Slight desquamation was noted in all animals at the end of the observation period.

In an eye irritation study in rabbits, mild to moderate conjunctival irritation and limited corneal and iridial effects were noted. However, the scores did not warrant classification of the chemical as an eye irritant. All treated eyes appeared normal within 7 days.

Sensitisation.
The notified chemical (at 100% induction concentration; 100% and 75% challenge concentration) was found to be a sensitiser in guinea pigs (Magnusson-Kligman method). Discrete/patchy erythema to intense erythema/swelling (or severe desquamation preventing an erythema reading) was noted in 16/19 and 14/19 animals (100% challenge concentration) and 14/19 and 11/19 animals (75% concentration), at 24 and 48 hours after patch removal, respectively. At rechallenge (50%, 25% and 10% notified chemical), erythema of similar severity and frequency (or severe desquamation preventing an erythema reading) were noted. In this study, no skin reactions were noted at challenge in animals in the control group.

In a dermal sensitisation study in guinea pigs (Buehler method), the notified chemical (at 100% induction concentration; 100% challenge concentration) was determined by the study authors to be a non-sensitiser. Very faint erythema was noted in 9/20 and 4/20 animals, at 24 and 48 hours after patch removal, respectively. However, a similar incidence and severity of erythema was noted for animals in the control group.

A structurally similar analogue of the notified chemical is classified with the risk phrase R43: May cause sensitisation by skin contact. Based on a weight-of-evidence the notified chemical is considered to be a sensitiser.

The notified chemical (at 1% concentration) was not a skin sensitiser in a human repeat insult patch study.

Repeated Dose Toxicity/Carcinogenicity.
No repeated dose toxicity data were provided for the notified chemical. However, a NOAEL of 25 mg/kg bw/day was established in a 13-week oral toxicity study (administration via drinking water) of a structurally similar analogue chemical in rats, based on effects on the hematopoietic system at higher concentrations.

A structurally similar analogue of the notified chemical is classified with the risk phrase R40: Limited evidence of a carcinogenic effect. While the potential for this effect to be associated with the notified chemical cannot be ruled out, it is noted that while the mechanism of tumour formation has not been fully elucidated, the tumours were not considered to have occurred via a direct genotoxic mechanism and a weight of evidence suggested that the chemical is likely to be non-genotoxic. In addition, the exposure concentrations that resulted in tumour formation in rats and mice in chronic inhalation toxicity studies were higher than the exposure concentrations that resulted in non-tumour effects.

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

Health hazard classification
Based on the data provided, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

R22 Harmful if swallowed
R38 Irritating to skin
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 ≤0.5% concentration) may occur during blending operations. While the notified chemical is considered to be harmful to human health via the oral and dermal routes and was found to be irritating to the skin and a skin sensitiser, ingestion is unlikely under the occupational settings described and the notified chemical will be present at concentrations below the cut-offs for these effects (NOHSC, 2004). Based on the potential carcinogenicity of a structurally similar analogue of the notified chemical, and given the absence of supporting studies on the notified chemical, 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.

Based on the information available, the risk to workers associated with the use of the notified chemical at ≤0.002% concentration in fine fragrances, ≤0.02% in other cosmetic products and ≤0.5% in household products, is not considered to be unreasonable.

6.3.2. Public Health

Dermal sensitisation
A significant risk associated with use of the notified chemical at ≤0.002% concentration in fine fragrances, ≤0.02% in other cosmetic products and ≤0.5% in household products, is its potential to cause sensitisation by skin contact.

Methods for the quantitative risk assessment for dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using face cream (containing 0.02% 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 0.55 μg/cm^2 (SCCS, 2010). When tested at 1% concentration in a human repeat insult patch study (0.2 mL applied to a 2 cm x 2 cm patch), the notified chemical was not a skin sensitiser. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 1.5 μg/cm^2. In this instance, the factors employed included an intraspecies factor (10), a matrix factor (3.16), a use and time factor (3.16) and a database uncertainty 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 face cream (a worst case example of a leave-on cosmetic product) at ≤0.02% concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level for rinse-off products (containing ≤0.02% notified chemical) and household products (≤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.
Repeated-dose toxicity
Repeat dose toxicity data are not available for the notified chemical. However, based on the observation of adverse effects in studies conducted on an analogue chemical, including carcinogenicity, similar effects for the notified chemical cannot be excluded.

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.093 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 25 mg/kg bw/day, which was established in toxicity studies on an analogue chemical. A MoE value ≥100 is considered acceptable to account for intra- and inter-species differences. Using the abovementioned NOAEL, a MoE of 270 was estimated, which is considered acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤0.002% concentration in fine fragrances, ≤0.02% in other cosmetic products and ≤0.2% 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 (≤0.5%) for local reformulation into a variety of consumer products (cosmetics, household products, fine fragrances). Releases during the reformulation processes at various sites throughout Australia are expected to be limited to traces of spills, formulation equipment cleaning and residues in empty packaging. Less than 0.1% of the total annual import volume of notified chemical is expected to remain as residues in import containers. The empty containers will eventually be recycled or disposed of to landfill. At the end of the reformulation run, the formulating and packing equipment will be washed and it is anticipated that the washings will be included in the next batch.

Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the sewer in domestic situations across Australia as a result of its use in cosmetic, toiletries and household 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 consumer containers are likely to be disposed of through domestic garbage disposal and enter landfill or be recycled.

7.1.2. Environmental Fate

The notified chemical is potentially volatile and may volatilise to air during use or sewage treatment. The half-life of the notified chemical in air is calculated to be 23.55 h based on reaction with hydroxyl radicals (AOPWIN, v1.92, US EPA, 2009). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will enter the sewer system as a result of the use of this chemical as component of fragrance preparations such as cosmetic and household care products. The notified chemical is not readily biodegradable (8% biodegradation after 28 days, OECD TG 301) and, based on its low adsorption coefficient (log K_{OC} = 2.00), only limited partitioning to sludge is expected. Most of the notified chemical is expected to remain in the water phase, due to its high water solubility (2.54 g/L at 20 °C), and may be released from sewage treatment plants to receiving waters, where it will disperse and eventually degrade. It has low potential to bioaccumulate, based on its low octanol/water partition coefficient (log K_{OW} = 2.31) and its low bioconcentration factor (log BCF = 1.19) predicted by a regression-based method based on the measured partition coefficient (BCFBAF v3.00; US EPA, 2009). A significant proportion of the notified chemical may be applied to land when effluent is used for irrigation, and residues in empty containers are expected to be disposed of to landfill. The notified chemical in landfill, soil and sludge are likely to be mobile. The notified chemical is expected to degrade through biotic or abiotic processes to form water and oxides of carbon and nitrogen.

For the details of the environmental fate studies please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

Since most of the polymer will be washed into the sewer, under a worst case scenario, with no removal of the notified polymer in the sewage treatment plant (STP), 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	1000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1000	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%	Mitigation
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

The notified chemical that is not removed from waste water during STP processes may be released to the environment in STP effluent. 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

No ecotoxicity data were submitted. As there is the potential for high aquatic exposure from the use and disposal of the notified chemical, modelled estimates for ecotoxicological endpoints for the notified chemical were calculated (ECOSAR (v1.00), Aliphatic amines class, user entered log Kow = 2.31; US EPA, 2009) and are tabulated below.

Endpoint	*Result*	*Assessment Conclusion*
Acute Toxicity		
Fish	96 h LC50 = 14.77 mg/L	Predicted to be harmful to fish
Daphnia	48 h EC50 = 1.58 mg/L	Predicted toxic to aquatic invertebrates
Algae	96 h EC50 = 0.75 mg/L	Predicted very toxic to algae

The modelled endpoints used here were derived from the aliphatic amines class of ECOSAR, which was the class of best fit for the notified chemical, and are considered useful to provide a general indication of potential environmental effects for the notified chemical. However, given the variation between the functional groups of the notified chemical to chemicals of the aliphatic amine class, these modelled endpoints are not considered sufficient to formally classify the acute and long term hazard under the Globally Harmonised System for the Classification and Labelling of Chemicals (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the estimated acute algal toxicity of the notified chemical and an assessment factor of 500. A more conservative assessment factor of 500 is appropriate, in this case, as although acute endpoints for three trophic levels are available as a general indication of potential toxicity, these endpoints are modelled estimates from a classed-based model which is not wholly representative of the structure of the notified chemical.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
Acute Algal toxicity	0.75 mg/L
Assessment Factor	500
PNEC:	1.50 µg/L

7.3. Environmental Risk Assessment

Based on the above PEC and PNEC, the following Risk Quotient has been calculated.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	1.50	0.40
Q - Ocean	0.06	1.50	0.04

The risk quotient for discharge of effluents containing the notified chemical to the aquatic environment, assuming a worst case with no removal during sewage treatment plant (STP) processes, indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The notified chemical has a low potential for bioaccumulation and is unlikely to be persistent in the environment. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point <-20 ºC

Method OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Determined by placing a test tube containing the test substance in a dry ice/acetone bath until the temperature of the substance reached ~-20 ºC. The test substance became increasingly viscous during cooling.
Test Facility Safepharm (2002a)

Boiling Point 192 ± 0.5 ºC at 99.97-100.17 kPa

Method OECD TG 103 Boiling Point.
EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Determined by differential scanning calorimetry (DSC).
Test Facility Safepharm (2002a)

Water Solubility 2.54 g/L at 20 ºC

Method OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Measured according to flask method 105 in solution pH 6.8. An aliquot (1.0035 g) of notified chemical was diluted to 100 mL using double distilled water in a flask. The contents of the flask were shaken at approximately 30 ºC and left standing at 20 ºC for 24 hours. After centrifugation at 6000 rpm for 15 minutes, the supernatant solution was analysed for the notified chemical by HPLC.
Test Facility Safepharm (2002a)

Hydrolysis as a Function of pH ≤35% at pH 7-12 and ≥55% at pH 2-6 at 40 ºC, 28 days

Method In-house

pH	*% hydrolysis after 7 days at 40ºC**	*% hydrolysis after 28 days at 40ºC**
2	>90	100
6	>35	>50
7	<10	~20
8.5	<5	<5
12	~10	~30

* Data points are approximated based on the provided graph

Remarks 0.001 M notified chemical in buffer solutions (types A, C, D, F and I: Reference hand book of Chemistry and Physics) with 1% non-ionic surfactant GC-FID determination at day 1, 2, 4, 7, 15, 21 and 28.

The rate of hydrolysis was negligible at pH 8.5 and increased under acidic conditions. Hydrolysis was approximately ≥55% under acidic conditions (pH 2-6) and ≤35% under basic or neutral conditions after 28 days at 40 ºC. This indicates that the notified chemical has potential to hydrolyse under acidic environment conditions.
Test Facility Firmenich (2011)

Partition Coefficient (n-octanol/water) log Pow = 2.31 at 20 ºC

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks Determination using the HPLC Method. Partition co-efficient was calculated as log Pow from calibration curve of retention time data and reference standard solutions.
Test Facility Safepharm (2002a)

Flash Point 81 ± 2 ºC at 101.3 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Determined using a closed cup equilibrium method.
Test Facility	Safepharm (2002b)

Autoignition Temperature 310 ± 5 °C

Method	Internal non-GLP method
Remarks	Determined by heating aliquots of the test material in a flask and observing any ignition.
Test Facility	Firmenich (2003)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
- Species/Strain: Rat/Sprague-Dawley CD
- Vehicle: Arachis oil BP
- Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	3F	2,000	3/3
II	3F	200	0/3
III	3M	200	0/3

- LD50: Between 200 and 2,000 mg/kg bw
- Remarks - Results: The mortalities occurred within a single day of dosing.
- Signs of Toxicity: Hunched posture was noted in all animals. In addition, signs noted in Group I and III treated animals included a comatose state (single group I animal), lethargy, ataxia, decreased respiratory rate, laboured respiration, ptosis and splayed gait. Surviving animals recovered within 1 day of dosing.
- Effects in Organs: Effects noted in group I animals included haemorrhagic or abnormally red lungs, dark liver, dark kidneys and haemorrhagic small intestine. No abnormalities were noted in animals of groups II and III.

CONCLUSION: The notified chemical is harmful via the oral route.

TEST FACILITY: Safepharm (2002c)

B.2. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion.
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 3
- Vehicle: None
- Observation Period: 7 days
- Type of Dressing: Semi-occlusive.
- Remarks - Method: One rabbit was initially treated at 3 test sites with exposure periods of 3 minutes, 1 hour and 4 hours. Two additional animals were then treated with a single application (4-hour exposure).

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	2	1.3	2	2	<7 days	0
Oedema	2	1	2	2	<7 days	0

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

- Remarks - Results: No evidence of skin irritation was noted following the 3-minute exposure period. Effects noted following the 1-hour exposure period included very

slight erythema (up to and including the 72-hour observation), a loss of skin elasticity (at the 72-hour observation) and slight desquamation (at Day 7). Following the 4-hour exposure period, very slight to well-defined erythema and very slight to slight oedema were noted (at up to and including the 72-hour observation). In addition, a loss of skin elasticity and/or flexibility was reported (at the 48 and 72-hour observations) and slight desquamation was noted in all treated animals at the end of the observation period.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY Safepharm (2002d)

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 3
Observation Period 7 days
Remarks - Method One drop of local anaesthetic (amethocaine hydrochloride, 0.5%) was instilled into both eyes of the third animal 1-2 minutes before treatment.

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	1.7	1.7	0.3	2	<7 days	0
Conjunctiva: chemosis	1.7	0.7	0	2	<7 days	0
Conjunctiva: discharge	1.7	0.7	0.3	3	<7 days	0
Corneal opacity	0.7	0	0	1	<72 hours	0
Iridial inflammation	1	0	0	1	<7 days	0

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

Remarks - Results Slight corneal and/or iridial effects were noted in the eyes of all treated animals 1-hour post instillation, with the effects persisting in the eye of a single animal only. Minimal to moderate conjunctival irritation was noted in the treated eyes of all animals, with all eyes appearing normal within 7 days.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Safepharm (2002e)

B.4. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – Magnusson and Kligman guinea pig maximisation test.
Species/Strain Guinea pig/Dunkin Hartley
PRELIMINARY STUDY Mild-moderate irritating Concentration:
intradermal: 5%
topical: 100%
MAIN STUDY
Number of Animals Test Group: 20M Control Group: 10M

INDUCTION PHASE

Induction Concentration:
intradermal: 5%
topical: 100%

Signs of Irritation

Following the intradermal and topical induction phases, minimal-moderate irritation at the induction sites was noted.

CHALLENGE PHASE

1st challenge

topical: 100% and 75%

2nd challenge

topical: 50%, 25% and 10%

Remarks - Method

The vehicle was arachis oil BP.

As the results of the first challenge indicated that the test substance was a sensitiser, the animals were rechallenged 11 days after the original application (at 50% and 25%) and then again 10 days after the original rechallenge (at 10%).

At rechallenge, the control groups consisted of 10 animals that had not been previously exposed to the test material, but had received intradermal injections of Freunds Complete Adjuvant and had formed part of a previous study on an unrelated test material.

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	100%	16/19	14/19	-	-
	75%	14/19	11/19	-	-
	50%	-	-	19/19	15/19
	25%	-	-	17/19	12/19
	10%			19/19	14/19
Control Group	100/75%	0/10	0/10	-	-
	50/25/10%	-	-	0/10	0/10

Remarks - Results

A single animal in the test group was found dead on day 11 of the study, with the cause of death not determined.

At challenge, discrete/patchy erythema to intense erythema/swelling was noted in 16/19 and 8/19 animals (treated with 100% test substance) and 14/19 and 10/19 animals (at 75% concentration), at 24 and 48 hours after patch removal, respectively. Severe desquamation prevented the evaluation of the erythema at the test sites of an additional 6/19 (100% concentration) and 1/19 (75% concentration) animals, 48 hours after patch removal.

At rechallenge, discrete/patchy erythema to intense erythema/swelling was noted in 19/19 and 9/19 animals (treated with 50% test substance) and 17/19 and 12/19 animals (at 25% concentration), at 24 and 48 hours after patch removal, respectively. Severe desquamation prevented the evaluation of the erythema at the test sites of an additional 6/19 (100% concentration) and 5/19 (75% concentration) animals, 48 hours after patch removal.

At rechallenge at 10% concentration, discrete/patchy erythema to moderate/confluent erythema was noted in 18/19 and 2/19 animals, at 24 and 48 hours after patch removal, respectively. Adverse reactions (severe desquamation and/or scab formation) prevented the evaluation of the erythema at the test sites of an additional 1/19 and 12/19 animals, at 24 and 48 hours after patch removal, respectively.

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

TEST FACILITY Safepharm (2002f)

B.5. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 406 Skin Sensitisation – Buehler test.
Species/Strain Guinea pig/Hartley
PRELIMINARY STUDY Maximum Non-irritating Concentration:
topical: 100%
MAIN STUDY
Number of Animals Test Group: 20M Control Group: 10M
INDUCTION PHASE Induction Concentration:
topical: 100%
Signs of Irritation During the induction phase, minimal irritation at the induction sites was noted.
CHALLENGE PHASE
1st challenge topical: 100%
Remarks - Method The vehicle was diethyl phthalate.

During the induction phase, patches containing the test substance were applied to each animal 3 times per week for 3 weeks. Patches were removed after 6 hours.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	100%	9/20	4/20
Control Group	100%	4/10	2/10

Remarks - Results At challenge, very faint erythema was noted in 9/20 and 4/20 animals, at 24 and 48 hours after patch removal, respectively. As a similar incidence and severity of erythema was noted for animals in the control group, the notified chemical was determined by the study authors to be non-sensitising under the conditions of the test.

CONCLUSION The notified chemical may have skin sensitising ability. However, the test conditions employed were inadequate and/or not sufficiently documented to enable a conclusion to be made.

TEST FACILITY PSL (2002)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (1% in vehicle)

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 h and graded after an additional 24 h (or 48 h 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 h. Sites were graded 24 and 48 h post-patch removal.
Study Group	99 F, 17 M; age range 22-70 years
Vehicle	Diethyl phthalate
Remarks - Method	Occluded. The test substance was spread on a 2 cm x 2 cm patch.

RESULTS

Remarks - Results	105/116 subjects completed the study. 5/116 subjects were discontinued for failure to keep to the scheduled visits (no induction observations were recorded for 4 of these subjects) and 3/116 subjects voluntarily withdrew (prior to the first or fourth induction readings). In addition, 3/116 subjects were discontinued due to non-product-related adverse events. A minimal or doubtful response was noted for 1 subject at the second induction observation. No adverse responses were noted at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (2002)

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	Phenobarbitone/β-naphthoflavone-induced rat liver (S9 homogenate)
Concentration Range in Main Test	a) With metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 0, 50, 150, 500, 1500, 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 only). Tests 1 and 2 were conducted on separate days using fresh cultures of the bacterial strains and fresh test material formulations. Vehicle and positive controls were used in parallel with the test material. Positive controls: i) without S9: N-ethyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535), mitomycin C (TA102), 9-aminoacridine (TA1537) and 4-nitroquinoline-1-oxide (TA98); ii) with S9: 2-aminoanthracene (TA100, TA1535, TA1537), benzo(a)pyrene (TA98) and 1,8-Dihydroxyanthraquinone (TA102).

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	>5,000	Negative
Test 2		>5,000	>5,000	Negative
Present				
Test 1	>5,000	>5,000	>5,000	Negative
Test 2		>5,000	>5,000	Negative

Remarks - Results	No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains up to and including the maximum dose, either with or 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	Safepharm (2001)

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