File No: LTD/1579

March 2012

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Doremox

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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL: + 61 2 8577 8800	
FAX: + 61 2 8577 8888	
Website:	www.nicnas.gov.au

Director
NICNAS

TABLE OF CONTENTS

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/1579	Firmenich Limited	Doremox	Yes	≤1 tonne per annum	Component of cosmetic and household products

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]. The classification and labelling details are:

R38 Irritating to skin
R43 May cause sensitisation by skin contact

and

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2009) is presented below. The environmental classification under this system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	*Hazard statement*
Skin Corrosion/Irritation	Category 2	Causes skin irritation
Skin Sensitisation	Category 1	May cause an allergic skin reaction
Aquatic Environment	Acute Category 2 Chronic Category 2	Toxic to aquatic life Toxic to aquatic life with long term effects

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

When used 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, maximum import volume and the assessed use pattern, the notified chemical is not considered to pose a 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:
  - 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. ≥20%: 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.

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 sensitisation.

CONTROL MEASURES

Occupational Health and Safety

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

- Employers should implement the following safe work practices to minimise occupational exposure to the notified chemical during reformulation processes:
  - 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 during reformulation processes:
  - Coveralls, impervious gloves, goggles

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill. Emergency procedures

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

Regulatory Obligations

Secondary Notification

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

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

(1) Under Section 64(1) of the Act; if
  - the importation volume exceeds one tonne per annum notified chemical;
  - the concentration of the chemical exceeds or is intended to exceed 0.01% in fine fragrances, 0.05% in other cosmetic products and 0.1% in household cleaning 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.

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 and additives/adjuvants.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low volume chemical permit

NOTIFICATION IN OTHER COUNTRIES
Switzerland (2006), USA (1998), Canada (2004), Phillipines (2000)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Doremox

MOLECULAR WEIGHT
Mn <500 Da

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

3. COMPOSITION

DEGREE OF PURITY ≥95%

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	252 ± 2 ºC at 97.7 kPa	Measured
Density	989 kg/m^3 at 20 ºC	Measured
Vapour Pressure	3.26 x 10^{-3} kPa at 25 ºC	Estimated – mean VP of Antoine & Grain methods with user input of boiling point, 252°C (US EPA, 2009)
Water Solubility	0.213 g/L at 20 ºC	Measured
Hydrolysis as a Function of pH	≤10% after 29 days at 40 ºC, pH 2-12	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.43	Measured
Adsorption/Desorption	log K_{oc} = 2.73	Estimated – from log Kow, user entered 3.43 (KOCWIN v2.00, US EPA, 2009)
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	114 ± 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	>114 °C based on flash point	Not expected to autoignite under normal conditions
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidative properties

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

Reactivity
Expected to be stable under normal conditions.

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 as a component of compounded fragrance preparations at ≤5% concentration.

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 RECIPIENT
Firmenich Limited

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

USE
The notified chemical will be used as a component of fragrances for a variety of cosmetic and household products, including fine fragrances (at ≤0.01% concentration), cosmetics (at ≤0.05%) and household cleaning products (at ≤0.1%).

OPERATION DESCRIPTION
The compounded fragrance preparations (containing ≤5% notified chemical) will be used in the formulation of perfumes, cosmetics and household cleaning products. The process will likely vary depending on the nature of the product formulated and may involve both automated and manual transfer steps. However, in general, the process is expected to involve a highly automated blending operation, followed by automated filling of containers of various sizes.

The final consumer products will be distributed to retail outlets, displayed and sold to consumers and professionals such as hairdressers, beauty salon workers 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 Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	4	Unknown	Unknown
Mixer	5	4	2
Drum handler	5	4	2
Drum cleaner	8	4	2
Maintenance	5	4	2
Quality control	1	0.5	1
Packaging	10	4	2
Salon workers	Unspecified	Unspecified	Unspecified
Cleaners	Unspecified	Unspecified	Unspecified

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical, as a component of the imported compounded fragrances (at ≤5%) or end-use products (at ≤0.1%), only in the event of accidental rupture of containers.

During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤5% concentration) may occur during manual transfer and weighing, blending, quality control analysis, and cleaning and maintaining of equipment. Exposure is expected to be minimised through the use of mechanical ventilation and enclosed systems, and through the use of personal protective equipment (PPE) such as coveralls, safety glasses and impervious gloves.

Exposure to the notified chemical in end-use products (at ≤0.1% concentration) may occur in professions where the services provided involve the application of cosmetic 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
End-use products will be sold to the general public and users will be repeatedly exposed to the notified

chemical through the use of fine fragrances (at ≤0.01%), cosmetics (at ≤0.05%) and household cleaning products (at ≤0.1%). The main 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 table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 >2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw; low toxicity
Rabbit, skin irritation	Irritating
Guinea pig, skin sensitisation – non-adjuvant test.	Evidence of sensitisation
Human repeat insult patch test (HRIPT)	No evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics, metabolism and distribution.
No toxicokinetic data on the notified chemical were submitted. Absorption of the notified chemical through the skin and gastrointestinal tract is expected based on the partition coefficient (3.43), water solubility (0.213 g/L) and low molecular weight (<500 Da). The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
The notified chemical was found to have low acute oral (LD50>2000 mg/kg bw) and dermal toxicity (LD50>2000 mg/kg bw) in rats. No acute inhalation toxicity data on the notified chemical was provided.

Irritation and Sensitisation.
The notified chemical was irritating to the skin of rabbits, with well-defined to moderate/severe erythema and slight to moderate oedema noted.

No eye irritation data were provided for the notified chemical. However, the notifier has classified the notified chemical with the risk phrase R36: Irritating to eyes.

The notified chemical was determined to be a skin sensitiser in guinea pigs (Buehler test in guinea pigs; 25% induction concentration and 12.5% and 25% challenge), with a greater incidence and severity of erythema noted following challenge. The notified chemical at 5% concentration was not a skin sensitiser in a human repeat insult patch test (HRIPT).

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

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 classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrases:

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
The main toxicological effects of concern are skin and eye irritation, and skin sensitisation. There is a potential for exposure to the notified chemical during reformulation processes (at ≤5% concentration). At such concentrations, and based on the 20% cut-off for eye and skin irritants set by the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), the risk of skin and eye irritation is not considered to be unreasonable. However, the potential for skin sensitisation is of concern, therefore caution should be exercised

when handling the notified chemical at >1% concentration during reformulation processes.

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

End-use
Exposure to the notified chemical in end-use products (at ≤0.1% concentration) may occur to professionals such as hair dressers, beauty salon workers or cleaners. The risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using the products (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 ≤0.01% concentration in fine fragrances, ≤0.05% in cosmetic products and ≤0.1% in household cleaning products, is not considered to be unreasonable.

6.3.2. Public Health

Members of the public may experience repeated exposure to the notified chemical through use of fine fragrances (≤0.01%), cosmetics (≤0.05%) and household cleaning products (≤0.1%). The repeated dose toxicity effects of the notified chemical have not been determined; however, based on the low concentration of notified chemical in end-use products, exposure to the notified chemical is expected to be limited. In addition, based on the low concentration, the risk of skin and eye irritation is not considered to be unreasonable.

The potential for skin sensitisation is the main concern associated with use of products containing the notified chemical. 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 0.05% 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 1.36 μg/cm^2 (SCCS, 2010). When tested at 5% concentration in a HRIPT study (0.2 mL applied to a 2 cm × 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 8.3 μg/cm^2. The safety 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 ≤0.05% concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level for rinse-off products (containing ≤0.05% notified chemical) and household cleaning products (≤0.1% 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.

Based on the information available, the risk to the public associated with the use of the notified chemical at ≤0.01% concentration in fine fragrances, ≤0.05% in other cosmetic products and ≤0.1% in household cleaning products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance preparations for local reformulation into a variety of consumer products (fine fragrances, cosmetics and household cleaning products). Release during reformulation in Australia is expected to arise from spills (0.1%), formulation equipment cleaning (no release estimate as cleaning water is recycled) and residues in import containers (0.1%). Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill. Import containers will either be recycled or disposed of through an approved waste management facility. Therefore, up to 0.2% of the import volume is estimated to be released to landfill as a result of reformulation in Australia.

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

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

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. The provided study indicates that the notified chemical is hydrolytically stable under environmental conditions. The notified chemical is predicted to be not readily biodegradable (BIOWIN v4.10, US EPA, 2009). Further modelling calculated the primary half-life of the notified chemical to be 3 months and 28 days (OASIS Catalogic v5.10.9, CATALOGIC_BOD 28 Days MITI (OECD 301C), v0.3.04). Therefore, in the absence of measured data, the notified chemical is considered to have the potential to persist in the environment. Although the notified chemical has a moderate partition coefficient (log Pow = 3.43) the notified chemical is not likely to bioaccumulate based on its predicted low bioconcentration factor (log BCF = 1.93, regression-based estimate, user entered log Kow = 3.43, BCFBAF v3.00, US EPA 2009). A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Despite having moderate water solubility, notified chemical residues in landfill and soils are expected to have low mobility based on its predicted soil adsorption coefficient (log Koc = 2.73). In the aquatic and soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile (log H = 0.43 Pa/m^3/mol, SimpleTreat, European Commission, 2003) and may volatilise to air during use or STP processes. The half-life of the notified chemical in air is calculated to be 3.7 h based on reactions 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 atmospheric compartment.

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	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 0.606 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 measured ecotoxicity data were submitted. As there is the potential for aquatic exposure from the use and disposal of the notified chemical, modelled estimates for ecotoxicological endpoints for the notified chemical have been calculated and are tabulated below.

Endpoint	*Result*	*Assessment Conclusion*
Acute		
Fish Toxicity	96 h LC50 = 7.50 mg/L[1]	Toxic to fish
Daphnia Toxicity	48 h EC50 = 5.22 mg/L[1]	Toxic to aquatic invertebrates
Algal Toxicity	96 h EC50 = 4.61 mg/L[1]	Toxic to algae
Chronic		
Fish Toxicity	30 d ChV = 0.859 mg/L[1]	Toxic to fish with long lasting effects
Daphnia Toxicity	ChV = 0.759 mg/L[1]	Toxic to aquatic invertebrates with long lasting effects
Algal Toxicity	ChV = 2.24 mg/L[1]	Not classified for long term hazard

[1] Modelled estimates (ECOSAR v1.00, class – neutral organics, user-entered log Kow = 3.43, US EPA, 2011).

The ecotoxicity endpoints were generated using validated quantitative structure activity relationships (QSARs) and the notified chemical is considered to be within the domain of the model and selected class. Therefore, the calculated QSAR results are considered reliable for the purposes of classification under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009). Based on the estimated endpoints in the absence of experimental data, the notified chemical is toxic to fish, aquatic invertebrates and algae, and is formally classified as 'Acute Category 2: Toxic to aquatic life'.

The GHS classification for long-term hazard are based on NOEC (or equivalent EC*x*) endpoints, whereas the available endpoints are chronic values [ChV = $(LOEC \times NOEC)^{½}$] which, by definition, are greater than the NOEC. On the basis of its lack of measured data to demonstrate rapid degradability and the estimated ChV endpoints, the notified chemical is, at best, toxic with long lasting effects to fish and aquatic invertebrates and not harmful with long lasting effects to algae. Based on the estimated endpoints in the absence of experimental data, the notified chemical is toxic to fish, aquatic invertebrates and algae, and is formally classified under the GHS as 'Chronic Category 2: Toxic to aquatic life with long lasting effects'.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the estimated daphnid chronic toxicity of the notified chemical and an assessment factor of 50. A more conservative assessment factor of 50 is appropriate in this case as although estimated chronic endpoints (ChV = $(LOEC \times NOEC)^{½}$) for three trophic levels are available, these chronic endpoints are not no-observed effect concentrations (NOECs).

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
ChV (Invertebrates)	0.76	mg/L
Assessment Factor	50	
PNEC:	15.18	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River	0.61	15.18	0.040
Q - Ocean	0.06	15.18	0.004

The risk quotient for discharge of effluents containing the notified chemical to the aquatic environment, assuming a worst case with no removal during 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, in the absence of measured data, it is considered to have the potential to persist in water and soils but is unlikely to be persistent in air. On the basis

of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point <-20 ºC

Method EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks The temperature of the test substance was lowered to ~ –20°C using a dry ice/isopropanol bath. The appearance of the test material remained unchanged.
Test Facility Firmenich (2006)

Boiling Point 252 ± 2 ºC at 97.7 kPa

Method EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Determined according to the Siwoloboff method.
Test Facility Firmenich (2006)

Density 989 kg/m^3 at 20 ºC

Method EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determined using an oscillating density meter.
Test Facility Firmenich (2006)

Water Solubility 0.213 g/L at 20 ºC

Method EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method with HPLC/UV analysis.
Test Facility Firmenich (2006)

Hydrolysis as a Function of pH ≤10% after 29 days at 40 ºC, pH 2-12

Method In-house

pH	*T (ºC)*	*% hydrolysis after 28 days**
2	40	≤10
5	40	≤10
7	40	~10
8.5	40	≤10
12	40	≤10

* Data points are approximated based on the provided graph

Remarks The notified chemical was dissolved in buffer solutions (types A, C, D, F and I: Reference Handbook of Chemistry and Physics) with 1% non-ionic surfactant. GC-FID determination at day 1, 2, 5, 8, 15, 20 and 29.

Hydrolysis was approximately equal to or less than 10% after 29 days storage at 40 ºC over the tested pH range (2-12). This indicates that the notified chemical is expected to be hydrolytically stable under environmental conditions (pH 4-9, 25 ºC), which is consistent with structural considerations.
Test Facility Firmenich (2011)

Partition Coefficient (n-octanol/water) log Pow = 3.43 at 20 ºC

Method EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks HPLC Method.
Test Facility Firmenich (2006)

Flash Point 114 ± 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 Firmenich (2006)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.
- Species/Strain: Rat/Crl:CD(SD)BR
- Vehicle: Corn oil
- Remarks - Method: No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 male	2000	0/5
II	5 female	2000	1/5

- LD50: >2000 mg/kg bw
- Remarks - Results: One female was killed *in extremis* on day 2.
- Signs of Toxicity: Hunched posture was noted on day 1 in 8/10 animals that reversed by day 3. Prostration was also noted for the single animal that was killed.
- Effects in Organs: Effects that were noted in the animal that was killed included a distended urinary bladder with black fluid and a pale liver and uterus. Effects noted in the remaining animals included incidences of redness of the lungs, thymus, stomach and kidneys and a white waxy plug within the urinary bladder. The study authors considered the necropsy findings not significant on the basis of low incidence or consistency with the background pathology of the rat strain.

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

TEST FACILITY: Toxicol (1992a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test
- Species/Strain: Rat/Crl:CD(SD)BR
- Vehicle: None
- Type of dressing: Semi-occlusive
- Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 male	2000	0/5
II	5 female	2000	0/5

- LD50: >2000 mg/kg bw
- Signs of Toxicity: None reported.
- Effects in Organs: Isolated incidences of red foci in the thymus, white waxy plug within the urinary bladder and urethra and a pale/thickened mucosa of the stomach were noted. The study authors considered the necropsy findings not significant on the basis of low incidence or consistency with the background pathology of the rat strain.

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

TEST FACILITY Toxicol (1992b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 4 females
Vehicle None
Observation Period 14 days
Type of Dressing Semi-occlusive
Remarks - Method No significant protocol deviations

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	2.6	3	14 days	2
Oedema	2.8	3	<14 days	0

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

Remarks - Results Well-defined to moderate/severe erythema and slight to moderate oedema were noted up to the day 7 observation. Slight to well-defined erythema remained at the day 14 observation. Desquamation was noted in all treated animals at day 7, which had resolved by day 14, with the exception of a single animal.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY Toxicol (1992c)

B.4. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 406 Skin Sensitisation – Buehler test
Species/Strain Guinea pig/Dunkin-Hartley albino
Vehicle Ethanol
PRELIMINARY STUDY Maximum Non-irritating Concentration:
Topical: 25% (very faint erythema was observed in 1/4 animals. The irritation observed at 50% was considered too severe for use of this concentration at induction in the main study).
MAIN STUDY
Number of Animals Test Group: 10 Control Group: 10
INDUCTION PHASE Induction Concentration: 25% (Days 1, 8 and 15)
Signs of Irritation Not reported.
CHALLENGE PHASE
1st challenge topical: 25% and 12.5% (day 28).
2nd challenge topical: 5% and 1% (day 37).
Remarks - Method There were only 10 animals in the treatment group.

As the results of the first challenge indicated that the test substance was a sensitiser, the animals were rechallenged (at 5% and 1%) to determine a concentration of the test substance which produced no apparent effect.

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	25%	8/10	9/10	-	-
	12.5%	8/10	9/10	-	-
	5%	-	-	1/10	1/10
	1%	-	-	1/10	0/10
Control Group	25%	3/9	5/9	-	-
	12.5%	1/9	1/9	-	-
	5%	-	-	3/9	2/9
	1%	-	-	0/9	0/9

Remarks - Results: One control animal was found dead on day 14. The increased incidence and severity of erythema in the test group, relative to the control group, observed during the first challenge was indicative of skin sensitisation.

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

TEST FACILITY: Toxicol (1992d)

B.5. Skin sensitisation – human volunteers

TEST SUBSTANCE: Notified chemical applied at 5% concentration

METHOD: Repeated insult patch test with challenge

Study Design: Induction Procedure: 9 induction applications made on Monday, Wednesday, Friday of three consecutive weeks. Skin was assessed 24 hours after patch removal (or 48 hours for patches applied on Friday).
Rest Period: Approximately 2 weeks.
Challenge Procedure: 1 challenge application to a naïve site, followed by skin assessment 24, 48 and 72 hours after patch removal.

Study Group: 105 (86 F, 19 M) ranging in age from 18-70 years.

Vehicle: 3:1 diethyl phthalate:ethanol

Remarks - Method: Occlusive 2×2 cm patches containing 0.2 mL of test material were held in place for 24 hours before removal by the applicants. 4 subjects voluntarily withdrew (no induction readings were noted for these subjects).

RESULTS

Remarks - Results: Scores of zero were observed at all induction and challenge observations indicating no irritation or sensitisation.

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

TEST FACILITY: TKL (1995)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 471 Bacterial Reverse Mutation Test – Plate Incorporation method.

Species/Strain: *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA$^-$

Metabolic Activation System: S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver

Concentration Range in Main Test: a) With metabolic activation: 0-5000 µg/plate
b) Without metabolic activation: 0-5000 µg/plate

Vehicle: Dimethyl sulfoxide

Remarks - Method: A preliminary toxicity test (0-5000 µg/plate) was performed to determine

the toxicity of the test material (TA100 and WP2uvrA$^-$ only).

Tests 1 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 (WP2uvrA$^-$, TA100, TA1535), 9-aminoacridine (TA1537) and 4-nitroquinoline-1-oxide (TA98); ii) with S9: 2-aminoanthracene (TA100, TA1535, TA1537, WP2uvrA$^-$) and benzo(a)pyrene (TA98).

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥500	≥500	>5000	Negative
Test 2	-	≥500	>5000	Negative
Present				
Test 1	≥1500	≥1500	>5000	Negative
Test 2	-	≥1500	>5000	Negative

Remarks - Results

In the mutation studies, the test substance caused a visible reduction in the growth of the bacterial background lawn to all strains, from 1500 and 500 µg/plate, with and without metabolic activation, respectively. Thus, the material was tested up to the toxic limit.

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 (2006)

BIBLIOGRAPHY

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA and Safford R (2008) Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. Regul. Toxicol. Pharm., 52:3-23.

European Commission (2003) Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances - Parts II and III.

Firmenich (2006) Doremox Determination of General Physico-Chemical Properties: Melting/Freezing Temperature, Boiling Temperature, Relative Density, Flash Point, Partition Coefficient and Water Solubility (Study No.: E046-05.2006, July, 2006). Geneva, Switzerland, Firmenich SA (Unpublished report submitted by the notifier).

Firmenich (2011) Stability Test of Perfumery Raw Materials, Stability Test – Doremox (11 October 2011). (Unpublished report submitted by the notifier).

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2001) National Code of Practice for the Storage and Handling of Workplace Dangerous Goods [NOHSC: 2017(2001)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

OASIS Catalogic v5.10.9. Laboratory of Mathematical Chemistry, Bulgaria.

NTC (National Transport Commission) 2007 Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), 7th Edition, Commonwealth of Australia.

RIVM (2010) Observations on the Methodology for Quantitative Risk Assessment of Dermal Allergens, Report 320015003/2010, National Institute for Public Health and the Environment.

Safepharm (2006) [Notified Chemical] Reverse Mutation Assay "Ames Test" Using *Salmonella Typhimurium* and *Eschereschia Coli* (SPL Project No.: 0161/0515, August, 2006). Derbyshire, UK, Safepharm Laboratories Limited (Unpublished report submitted by the notifier).

SCCS (2010) Notes of Guidance for testing of Cosmetic Ingredients and Their Safety Evaluation (7th revision) European Commission - Scientific Committee on Consumer Safety.

TKL (1995) Repeated Insult Patch Study (TKL Study No.: 951014, July, 1995). NJ, USA, TKL Research Inc. (Unpublished report submitted by the notifier).

Toxicol (1992a) [Notified Chemical] Acute Oral Toxicity Study in the Rat. (Study Ref. No.: A/O/33924, April, 1992). Herefordshire, UK, Toxicol Laboratories Limited (Unpublished report submitted by the notifier).

Toxicol (1992b) [Notified Chemical] Acute Dermal Toxicity Study in the Rat. (Study Ref. No.: A/O/33925. April, 1992). Herefordshire, UK, Toxicol Laboratories Limited (Unpublished report submitted by the notifier).

Toxicol (1992c) [Notified Chemical] Acute Dermal Irritation/Corrosion Study. (Study Ref. No.: A/S/33926, May, 1992). Herefordshire, UK, Toxicol Laboratories Limited (Unpublished report submitted by the notifier).

Toxicol (1992d) Delayed Dermal Sensitisation Study in the Guinea Pig [Notified Chemical]. (Study Ref. No.: A/B/33928, May, 1992). Herefordshire, UK, Toxicol Laboratories Limited (Unpublished report submitted by the notifier).

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS), 3rd revised edition. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >.

US EPA (2009) Estimations Programs Interface Suite™ for Microsoft® Windows, v 4.00. United States Environmental Protection Agency. Washington, DC, USA.

US EPA (2011) Estimations Programs Interface Suite™ for Microsoft® Windows, v 4.10. United States Environmental Protection Agency. Washington, DC, USA.