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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Davanate

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

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

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

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Director
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TABLE OF CONTENTS

SUMMARY 3
CONCLUSIONS AND REGULATORY OBLIGATIONS 3
ASSESSMENT DETAILS 6
1. APPLICANT AND NOTIFICATION DETAILS 6
2. IDENTITY OF CHEMICAL 6
3. COMPOSITION 6
4. PHYSICAL AND CHEMICAL PROPERTIES 6
5. INTRODUCTION AND USE INFORMATION 7
6. HUMAN HEALTH IMPLICATIONS 8
6.1. Exposure Assessment 8
6.1.1. Occupational Exposure 8
6.1.2. Public Exposure 9
6.2. Human Health Effects Assessment 9
6.3. Human Health Risk Characterisation 10
6.3.1. Occupational Health and Safety 10
6.3.2. Public Health 11
7. ENVIRONMENTAL IMPLICATIONS 12
7.1.1. Environmental Exposure 12
7.1.2. Environmental Fate 12
7.1.3. Predicted Environmental Concentration (PEC) 12
7.2. Environmental Effects Assessment 13
7.2.1. Predicted No-Effect Concentration 13
7.3. Environmental Risk Assessment 13
APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES 14
APPENDIX B: TOXICOLOGICAL INVESTIGATIONS 16
B.1. Acute toxicity – oral 16
B.2. Acute toxicity – dermal 16
B.3. Irritation – skin 17
B.4. Irritation – eye 17
B.5. Skin sensitisation – mouse local lymph node assay 18
B.6. Skin sensitisation – human volunteers 19
B.7. Repeat dose toxicity 19
B.8. Repeat dose toxicity 20
B.9. Genotoxicity – bacteria 21
B.10. Genotoxicity – in vitro 22
APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS 24
C.1. Environmental Fate 24
C.1.1. Ready biodegradability 24
C.2. Ecotoxicological Investigations 24
C.2.1. Acute toxicity to aquatic invertebrates 24
C.2.2. Algal growth inhibition test 25
C.2.3. Inhibition of microbial activity 26
BIBLIOGRAPHY 27

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1784	Firmenich Limited	Davanate	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Flammable liquids (Category 4)	H227 - Combustible liquid
Skin Sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

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

R38: Irritating to skin
R43: May cause sensitisation by skin contact

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

Hazard classification	*Hazard statement*
Acute (Category 3)	H 402 – Harmful to aquatic life

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

- The notified chemical should be classified as follows:
  - Skin Sensitisation (Category 1): H317 – May cause an allergic skin reaction

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

- Due to the combustible properties of the notified chemical, the notifier should consider their obligations under the Australian Dangerous Goods Code.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation:
  - Enclosed, automated processes, where possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation:
  - Avoid contact with skin and eyes

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Coveralls
  - Impervious gloves
  - Eye protection

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

- A copy of the (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

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

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, 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 0.1% in fine fragrances, 0.01% in other cosmetic products, 0.1% in air fresheners or 0.01% in household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Firmenich Limited (ABN: 86 002 964 794)
73 Kenneth Road
BALGOWLAH NSW 2093

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities and additives/adjuvants.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant and flammability limits

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA (2007), EU (2007), Switzerland (2008), Philippines (2009)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Davanate

MOLECULAR WEIGHT
< 200 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless liquid

Property	Value	Data Source/Justification
Freezing Point	< -20 °C	Measured
Boiling Point	175 °C at 100.97 kPa	Measured
Density	915 kg/m^3 at 20 °C	Measured
Vapour Pressure	0.017 kPa at 25 °C	Measured
Water Solubility	0.486 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Hydrolytically stable	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.36	Measured
Surface Tension	67.9 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.01	Measured
Dissociation Constant	Not determined	Does not contain dissociable functionalities

Property	Value	Data Source/Justification
Flash Point	63 ± 2 °C at 101.3 kPa	Measured
Autoignition Temperature	300 ± 5 °C	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidising properties.

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

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

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

Hazard classification	***Hazard statement***
Flammable liquids (Category 4)	H227 - Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia either: (1) in the neat form for formulation into fragrance preparations and end-use products; (2) as a component of fragrance preparations (at concentrations ≤ 1%) to be blended into end-use products; and/or (3) as a component of end-use products (at concentrations ≤ 0.1%).

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1

PORT OF ENTRY
Sydney, by wharf or airport

IDENTITY OF MANUFACTURER/RECIPIENTS
Firmenich Limited

TRANSPORTATION AND PACKAGING
The notified chemical in the neat form or as a component of fragrance preparations will be imported into Australia in lacquered drums of sizes ranging from 5 kg up to 180 kg. The end-use products (≤ 0.1% notified chemical) will be packaged in typical consumer-sized containers suitable for retail sale.

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

USE
The notified chemical will be used as a fragrance component in a variety of cosmetic and household products. Household products containing the notified chemical are expected to include air fresheners, all-purpose cleaners, detergents, fabric softeners, hard surface wipes, furniture/window cleaner, dish wash and lavatory care. The content in the final consumer products will vary, with the proposed usage concentrations of ≤ 0.1% for air fresheners and ≤ 0.01% for other household products, ≤ 0.1% for fine fragrances, and ≤ 0.01% for other cosmetic products including hair spray.

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

Reformulation
At the customer facilities, the notified chemical will be formulated into either a fragrance formula or end-use products. The reformulation procedure will likely vary depending on the nature of the product to be 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.

End-use
Household products containing the notified chemical (≤ 0.1% concentration) may be used by consumers and professional workers. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines, or open processes and manually applied by rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the household product will be diluted with water prior to application.

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

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

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

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the neat notified chemical, or as a component of the imported fragrance preparations (≤ 1% concentration) or end-use products (≤ 0.1% concentration), only in the event of accidental rupture of containers.

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

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through

the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection, impervious gloves and respiratory protection (if appropriate).

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤ 0.1% concentration) to clients (e.g. hair dressers, workers in beauty salons) or the use of household products (at ≤ 0.01% concentration) in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical through the use of cosmetic products (at ≤ 0.1% concentration), household products (at ≤ 0.01% concentration) and air fresheners (at ≤ 0.1% concentration). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

A combined internal dose of 0.0404 mg/kg bw/day was estimated using data on typical use patterns of cosmetic and household cleaning product categories in the which the notified chemical may be used (SCCS, 2010; Cadby *et al.,* 2002; SDA, 2005; specific use details of the notified chemical are considered as exempt informaiton). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic and household products that may contain the notified chemical.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (1%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 7 days	NOAEL = 1000 mg/kg bw/day
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non-mutagenic
Genotoxicity – in vitro chromosome aberration	non-clastogenic

Toxicokinetics
No information on the toxicokinetics of the notified chemical was provided. Based on the partition coefficient (log P_{ow} = 3.36) and the low molecular weight (< 200 Da) of the notified chemical, passive diffusion across the gastrointestinal tract (GI) and absorption across the skin may occur. The notified chemical may also be absorbed via the respiratory tract.

Acute toxicity.
The notified chemical was of low acute oral and dermal toxicity in rats. No acute inhalation toxicity data were provided for the notified chemical.

Irritation
The notified chemical was a skin irritant to rabbits. Well-defined erythema and slight oedema were observed in all three rabbits on day 3. Moderate desquamation was observed in two animals after 7 days, with slight desquamation persisting in one animal at the 14-day observation. The irritation scores did not warrant classification of the chemical as a skin irritant according to the *GHS*, as adopted for industrial chemicals in Australia, but did warrant classification of the chemical according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

The notified chemical was a slight eye irritant to rabbits.

Skin sensitisation
The notified chemical was an extremely weak skin sensitiser in a local lymph node assay (LLNA) in mice (EC3 = 41.6%). As the calculated EC3 value is beyond the dose range tested (i.e. > 40%), the study authors considered this value as unreliable. Based on the results of the study, an EC3 = 40% is therefore considered appropriate for risk assessment purposes. The notified chemical was not a skin sensitiser at 1% concentration in a human repeat insult patch test (HRIPT).

Repeated dose toxicity
In a 7-day repeated dose gavage study, rats (3/sex/dose) were treated at 0, 250, 500 or 1000 mg/kg bw/day. The NOAEL was established as 1000 mg/kg bw/day, based on the lack of treatment related adverse effects.

In a 28-day repeated dose gavage study, rats (5/sex/dose) were treated at 0, 30, 300 or 1000 mg/kg bw/day. The NOAEL was established as 1000 mg/kg bw/day, based on the lack of treatment related adverse effects.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic to human peripheral blood lymphocytes in an *in vitro* chromosome aberration study.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk 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
Transport and storage
Transport and storage workers are only expected to become exposed to the notified chemical (at ≤ 100% concentration) in situations of an accidental discharge, spill or leaking drum, requiring clean up. If such an event occurs, a worker may be exposed through dermal or ocular contact. Should these workers become exposed, skin and eye irritation, and skin sensitisation are possible.

The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective clothing, chemical resistant gloves, and eye protection. Therefore, provided adequate control measures are in place to minimise worker exposure, including PPE, the risk to transport and storage workers from use of the notified chemical (at ≤ 100% concentration) is not considered to be unreasonable.

Reformulation
Exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. At the proposed usage concentration, skin irritation, slight eye irritation and skin sensitisation may occur. Caution should therefore be exercised when handling the notified chemical during reformulation processes.

The use of mechanical ventilation and/or enclosed systems, and the use of PPE such as protective clothing, eye protection, impervious gloves and respiratory protection (if appropriate) are expected 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 reformulation workers from use of the notified chemical (at ≤ 100% concentration) is not considered to be unreasonable.

End-use
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤ 0.1% concentration) to clients (e.g. hair dressers, workers in beauty salons) or the use of household products (at ≤ 0.01% concentration) in the cleaning industry. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. For hairdressing salons, good ventilation would be recommended if hair spray is routinely used in a confined space. If PPE is used, the exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various cosmetic and household products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2.). Based on the information available, the risk to workers associated with use of the notified chemical in cosmetic (at ≤ 0.1% concentration) and household (at ≤ 0.01% concentration) products is not considered to be unreasonable.

6.3.2. Public Health
Members of the public may be repeatedly exposed to the notified chemical during the use of leave-on and rinse-off cosmetics (at ≤ 0.01% concentration), fine fragrances (at ≤ 0.1% concentration), household products (at ≤ 0.01% concentration) and air fresheners (at ≤ 0.1% concentration).

Systemic effects
The potential systemic exposure to the public from the use of the notified chemical in cosmetic and household products was estimated to be 0.0404 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 1000 mg/kg bw/day derived from a 28-day repeated dose toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 24,756. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. The risk to the public of systemic toxicity from use of the notified chemical (at ≤ 0.1% concentration) is therefore not considered to be unreasonable.

Skin sensitisation
There is a risk of potential skin sensitisation associated with the use of the notified chemical in cosmetics and household cleaning products at the proposed usage concentrations (at ≤ 0.1% concentration).

Proposed methods for the quantitative risk assessment of dermal sensitisation have been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using a fine fragrance (containing ≤ 0.1% notified chemical) as an example product that may contain the notified chemical, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 3.75 μg/cm^2 (Cadby *et al* 2002). When tested in an LLNA study, the notified chemical was a skin sensitiser with an EC3 value of 40%. Consideration of the study details and application of appropriate safety factors, allowed for the derivation of an Acceptable Exposure Level (AEL) of 30.5 μg/cm^2. In this instance, the factors employed included an interspecies factor (3), intra-species factor (10), a matrix factor (3.16), and a use and time factor (3.16), giving an overall safety factor of > 300 (300 used for calculations).

As the AEL > CEL, given the extremely weak sensitisation potency of the notified chemical, the risk to the public associated with the use of the notified chemical in fine fragrances (a worst case example of a cosmetic product) at ≤ 0.1% concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level for household products (≤ 0.01% 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.

Local effects
The notified chemical is an irritant to skin and a slight irritant to eyes. Irritation is not expected at the proposed usage concentrations. The risk to the public of skin and eye irritation from use of the notified chemical (at ≤ 0.1% concentration) is therefore not considered to be unreasonable.

Therefore, based on the information available, when used in the proposed manner the risk to the public associated with use of the notified chemical at ≤ 0.1% in fine fragrances, ≤ 0.01% in other cosmetic ingredients and household products and ≤ 0.1% for air fresheners is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia; therefore there is no release of the notified chemical to the environment from this activity. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

During reformulation processes, limited release of the notified chemical is expected from cleaning of equipment as washings will be reused. A total of up to 0.2% of the import volume is estimated to be generated as waste from residues in empty containers and spills during reformulation. Empty containers containing the notified chemical will either be recycled or disposed of through an approved waste management facility.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic and domestic products, which are washed off the hair and skin of consumers as well as from cleaning activities and disposed of to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. The containers are expected be disposed of through domestic garbage disposal and will enter landfill, or be subjected to recycling processes.

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 biodegradation study indicated that the notified chemical is considered to be rapidly degradable in the environment and hence, it is expected to be degraded during the wastewater treatment process. Based on its low adsorption coefficient value (log K_{oc} = 2.01), only limited partitioning to sludge is expected. The notified chemical has low potential to bioaccumulate based on its low partition coefficient (log Pow = 3.36). In surface waters, the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is expected to have high volatility from water (log H = 45 Pa/m^3/mol) and is likely to volatilise to air during use or sewage treatment based on calculations for a representative component of the notified chemical. In the event of release to the atmosphere, the notified chemical is not expected to persist in the air compartment based on calculations (AOPWIN v1.92; US EPA, 2011) for a representative component of the notified chemical.

A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have moderate mobility based on its low soil adsorption coefficient. 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.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the Predicted Environmental Concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleansing products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that 0% of the notified chemical will be removed during sewage treatment processes.

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 0.61 µg/L may potentially result in a soil concentration of approximately 4.0 µg/kg from each year of irrigation. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

Ecotoxicological data were submitted for the notified chemical. Details of the studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity (48 h)	EC50 = 27 mg/L	Harmful to aquatic invertebrates
Algal Toxicity (72 h)	E_rC50 = 25 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	EC50 (30 min) = 460 mg/L	Inhibitory to microbial respiration

The notified chemical is considered to be harmful to aquatic invertebrates and algae. On the basis of the acute toxicity data, the notified chemical is harmful to aquatic organisms. Therefore, Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009), the notified chemical is formally classified as Acute Category 3; Harmful to aquatic life. Based on its acute toxicity and ready biodegradability, the notified chemical has not been formally classified under GHS for chronic category.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (algae, E_rC50) for the notified chemical. Acute ecotoxicity endpoints for aquatic species from only two trophic levels are available. Therefore, an assessment factor of 1000 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga).	25	mg/L
Assessment Factor	1,000	
PNEC:	25	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.61	25	0.024
Q - Ocean:	0.06	25	0.002

The risk quotient for discharge containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its reported use pattern and annual importation quantity. The notified chemical has low potential for bioaccumulation. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import 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

Freezing Point < -20.0 ± 0.5 °C

Method EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks The test substance did not melt when cooled to -20.0 °C
Test Facility Safepharm (2007a)

Boiling Point 175± 0.5 °C at 100.97 kPa

Method EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Determined using differential scanning calorimetry.
Test Facility Safepharm (2007a)

Density 915 kg/m^3 at 20 °C

Method EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Pycnometer method
Test Facility Harlan (2010a)

Vapour Pressure 0.017 kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks The gas saturation method was used.
Test Facility Harlan (2010b)

Water Solubility 0.486 g/L at 20 °C

Method EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method
Test Facility SafePharm (2007a)

Hydrolysis as a Function of pH Hydrolytically unstable

Method Not reported

pH	*T (°C)*	*$t_{½}$ < days>*
2	25	Not reported
5	25	Not reported
7	25	Not reported
8.5	25	Not reported
12	25	Not reported

Remarks The concentration of the test substance after 28 days at 40 °C had decreased by about 30% at pH 8.5. The test substance is considered hydrolytically unstable under the environmental pH range of 4 to 9.
Test Facility Not reported

Partition Coefficient (n-octanol/water) log Pow = 3.36

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method/Flask Method
Test Facility Safepharm (2007a)

Surface Tension 69.7 mN/m at 20.2 ± 0.5 °C

Method EC Council Regulation No 440/2008 A.5 Surface Tension.

Remarks Ring method. Concentration: 0.408 g/L
Test Facility Harlan (2010a)

Adsorption/Desorption log K_{oc} = 2.01
– screening test

Method OECD 121: HPLC Screening Method
Remarks HPLC Method
Test Facility Harlan (2010c)

Flash Point 63 ± 2 °C at 101.3 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks A closed cup equilibrium method was used.
Test Facility Safepharm (2007b)

Autoignition Temperature 300 ± 5 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility Harlan (2010d)

Explosive Properties Predicted Negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Predicted negative based on chemical structure and oxygen balance.
Test Facility Harlan (2007a)

Oxidizing Properties Predicted Negative

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks Predicted negative based on chemical structure.
Test Facility Harlan (2010d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure
Species/Strain	Rat/Sprague-Dawley
Vehicle	None
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	2000	0/1
2	4 F	2000	0/4

LD50	> 2000 mg/kg bw
Signs of Toxicity	Hunched posture was observed in one female during the first four hours after dosing but was normal after 24 hours. Hunched posture, lethargy, ataxia, increased salivation, decreased respiratory rate, laboured respiration, and red/brown staining around the mouth was observed in another female during the first four hours.
Effects in Organs	No abnormalities detected.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm (2007c)

B.2. Acute toxicity – dermal

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

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	2000	0/3
2	3 F	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No signs of dermal irritation were observed.
Signs of Toxicity - Systemic	Depressed body weight gain or body weight loss was observed in two females over the first week of the observation period. Another two females gained weight over the first week of the observation period but did not gain weight during the second week.
Effects in Organs	No abnormalities detected.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Safepharm (2010a)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 males
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2.0	2.0	2.0	2	< 7 days	0
Oedema	2.0	2.0	2.0	2	< 7 days	0

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

Remarks - Results	Well-defined erythema (grade 2) and slight oedema (grade 2) were observed in all animals up to and including the 72-hour observation point. Light brown discolouration of the epidermis and loss of skin elasticity were observed at 72 hours in all animals. Moderate desquamation was observed in two animals after 7 days, with slight desquamation persisting in one animal at the 14-day observation.
CONCLUSION	The notified chemical is irritating to the skin.
TEST FACILITY	Safepharm (2007d)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 males
Observation Period	72 hours
Remarks - Method	No significant protocol deviations. A rabbit enucleated eye test (REET) was conducted prior to the main test. The corneas of three enucleated eyes from New Zealand White Rabbits were treated with 0.1 mL notified chemical and maintained at 32 °C. A control group of two enucleated eyes was treated with 0.9% sodium chloride. The eyes were assessed for corneal thickness (swelling), corneal opacity, alteration of the corneal epithelium and fluorescein uptake, for an observation period of 4 hours.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.7	1.0	0.7	2	< 72 h	0
Conjunctiva: chemosis	0.3	0.7	0.7	1	< 72 h	0
Conjunctiva: discharge	0	0.3	0.3	2	< 48 h	0
Corneal opacity	0	0	0	0	-	0

Iridial inflammation	0	0.3	0	1	< 48 h	0

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

Remarks - Results

The REET test indicated that the notified chemical was unlikely to be a severe occular irritant, based on similar observations in the measured parameters in treated and control groups.

In the main study, slight (grade 1) to moderate (grade 2) conjunctival redness and discharge were observed up to 48 hours. Slight conjunctival chemosis (grade 1) was observed up to 48 hours. Slight iridial inflammation (grade 1) was observed in all animals at 1 hour and in one animal at 24 hours. All eyes were normal after 72 hours.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Safepharm (2007e)

B.5. Skin sensitisation – mouse local lymph node assay

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain

Mouse/ CBA/J (female)

Vehicle

Acetone:olive oil (4:1)

Remarks - Method

The main study was conducted using 5 mice/group at 1, 5, 10, 20 or 40%. A vehicle control group was conducted using 8 mice/group. The study authors reported that the sponsor requested the tested dosing regime.

RESULTS

Concentration (%)	*Proliferative response (DPM)*	*Stimulation Index (Test/Control Ratio)*
Test substance		
0 (vehicle control)	37.7*	-
1	76.2	2.0
5	66.8	1.8
10	42.1	1.1
20	71.4	1.9
40	118.1	3.1
Positive control (isoeugenol)		
5	327.1	8.7
Positive control (HCA)		
15	91.2	2.4
60	376.1	10.0

*A single observation was excluded as an outlier in the vehicle control group.

Remarks - Results

There were no treatment related signs of systemic toxicity or irritation.

The stimulation index value was > 3 for the group treated with the notified chemical at 40% indicating the test substance is a sensitiser. The EC3 value was calculated to be 41.6%. However as this value is beyond the dose range tested the calculated EC3 value was considered unreliable by the study authors.

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

CONCLUSION

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

TEST FACILITY	BRT (2007)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (1% concentration)
METHOD	Repeated insult patch test with challenge
Study Design	Induction procedure: 9 induction applications made on Monday, Wednesday and Friday of three consecutive weeks. The subjects were required to remove the patches after 24 hours. The skin was assessed when the subject attended to have the next induction application. Subjects who missed an induction exposure received a make-up patch following the scheduled ninth exposure. Rest period: 10-15 days. Challenge procedure: The challenge exposure occurred during the sixth week of the study. Each subject received one challenge application to a naïve site and was required to remove the patch after 24 hours. The skin was assessed 24 and 48 hours after patch removal.
Study Group	113 (97 F, 16 M) subjects ranging in age from 18-70 years (mean 49 years). Subjects were included if they were in general good health and free of dermatological or systemic conditions. Subjects were excluded if they had any skin conditions (including atopic dermatitis or psoriasis), were pregnant or lactating, were currently taking medication that was considered to interfere with the study, or had any known sensitivities to topically applied products (cosmetics or medications).
Vehicle	diethyl phthalate:ethanol (3:1)
Remarks - Method	Patches containing 0.3 mL of test material (1% notified chemical) were applied to the infrascapular region of the back, secured with hypoallergenic tape. The patches were occluded under a 25 mm Hilltop Chamber lined with a non-woven cotton patch.
RESULTS	
Remarks - Results	Six subjects voluntarily withdrew from the study or were lost to follow up, all by the fifth induction application. Scores of zero were noted at all induction and challenge observations indicating no irritation or sensitisation under the conditions of the test.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (2010)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified Chemical
METHOD	No guideline stated, similar to OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 7 days
Vehicle	Arachis oil BP
Remarks - Method	In a 7 day repeated dose oral gavage study, rats (3/sex/dose) were treated with the notified chemical at 0, 250, 500 or 1000 mg/kg bw/day. Mortality, clinical signs of toxicity, body weight, and food and water consumption were recorded during the study. All animals were subject to gross necropsy.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	3 M + 3 F	0	0/6
low dose	3 M + 3 F	250	0/6
mid dose	3 M + 3 F	500	0/6
high dose	3 M + 3 F	1000	0/6

Clinical Observations

There were no treatment related clinical signs of toxicity. Increased salivation was observed shortly after dosing in animals treated with the test substance but was likely due to the gavage dosing method and was not attributed to test substance related toxicity. Body weight, body weight gain, and food and water consumption were similar in treated and control groups.

Effects in Organs

There were no gross abnormalities noted at necropsy.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the lack of treatment related adverse effects.

TEST FACILITY Safepharm (2010b)

B.8. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents

Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 M + 5 F	0	0/10
low dose	5 M + 5 F	30	0/10
mid dose	5 M + 5 F	300	0/10
high dose	5 M + 5 F	1000	0/10

Clinical Observations

There were no treatment related clinical signs of toxicity. Increased salivation was observed shortly after dosing in animals treated at 300 and 1000 mg/kg bw/day, but was likely due to the gavage dosing method and was not attributed to test substance related toxicity.

There were no treatment related findings in the weekly behavioural, functional or sensory reactivity assessments. There were statistically significant decreases in mean forelimb grip strength in all female treatment groups during week 2. Based on the transient nature and the lack of a dose response, this decrease is considered to be of low toxicological concern.

There were no treatment related changes in absolute body weights or body weight gain. There was a statistically significant reduction in the body weight gain in males treated at 1000 mg/kg bw/day during the fourth week. This finding was considered to be of low toxicological concern as there was no associated decrease in overall body weight gain over the duration of the study. Food and water consumption was similar in treated and control groups.

Laboratory Findings – Haematology and Clinical Chemistry

There were statistically significant decreases in mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration in all treated groups of males. In males treated at 1000 mg/kg bw/day, there was a statistically significant decrease in total leucocyte count with an associated statistically significant decrease in lymphocytes. These changes were reported as being within the expected normal range for this strain of rat, thus are considered to be of low toxicologically concern. Haematological parameters in females were unaffected.

In all male treatment groups, there were statistically significant decreases in albumin/globulin ratio, chloride and phosphorous, which are of low toxicological concern as they were reported to be within the expected normal range for this strain of rat. There were statistically significant decreases of calcium in all treated groups of males, but were not considered to be of toxicological concern due to the lack of a dose response. Clinical chemistry parameters in females were unaffected.

Effects in Organs

There were statistically significant increases in absolute and relative liver weights in males treated at 1000 mg/kg bw/day (↑3%/↑6% absolute/relative) and females treated at 300 (↑6%/↑6% absolute/relative) and 1000 mg/kg bw/day (↑7%/↑11% absolute/relative). Minimal to slight centrilobular hepatocellular hypertrophy was observed in males and females treated at 300 and 1000 mg/kg bw/day (see following Table).

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*30*	*300*	*1000*	*0*	*30*	*300*	*1000*
Centrilobular hepatocellular hypertrophy	0/5	0/5	2/5 (1.0)	5/5 (1.4)	0/5	0/5	4/5(1.3)	5/5 (1.4)

( ), Average severity of affected animals: 1=minimal, 2=slight, 3=moderate, 4=severe.

Remarks – Results

Treatment related findings of increased liver weights and hepatocellular hypertrophy were observed in males and females. These findings are commonly observed in toxicology studies, indicative of an adaptive response to a xenobiotic. In this study, the findings were of low magnitude and severity, with no accompanying clinical chemistry findings indicative of liver toxicity, thus are of low toxicological concern and are likely adaptive in nature.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the lack of toxicologically significant effects.

TEST FACILITY Safepharm (2010c)

B.9. 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
E. coli: WP2uvrA$^-$

Metabolic Activation System Phenobarbitone/β-naphthoflavone induced rat liver (S9 homogenate)

Concentration Range in Main Test a) With metabolic activation: 0, 15, 50, 150, 500, 1500, 5000 µg/plate
b) Without metabolic activation: 0, 15, 50, 150, 500, 1500, 5000 µg/plate

Vehicle Dimethyl sulfoxide

Remarks - Method No significant protocol deviations.

Vehicle and positive controls were conducted in parallel with the test material in accordance with the testing guideline.

RESULTS

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

Remarks - Results

No statistically or biologically 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 (2007f)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test

Cell Type/Cell Line: Human peripheral lymphocytes

Metabolic Activation System: Phenobarbitone/β-naphthoflavone induced rat liver (S9 homogenate)

Vehicle: Dimethyl sulfoxide

Remarks - Method: No significant protocol deviations.

Vehicle and positive controls were conducted in parallel with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 11.11, 22.2*, 44.4*, 88.8*, 177.75*, 355.5, MMC 0.4*	4 h	24 h
Test 2	0*, 22.2, 44.4, 88.8*, 177.75*, 266.55*, 355.5*, 711, MMC 0.2*	24 h	24 h
Present			
Test 1	0*, 22.2, 44.4*, 88.8*, 177.75*, 355.5*, 711 CP 5*	4 h	24 h
Test 2	0*, 22.2, 44.4*, 88.8*, 177.75*, 355.5*, 711, CP 5*	4 h	24 h

* Cultures selected for metaphase analysis.
MMC, Mitomycin C. CP, Cyclophosphamide.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	*Cytotoxicity**	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 355.5	none	negative
Test 2	≥ 355.5	none	negative
Present			
Test 1	≥ 711	none	negative
Test 2	≥ 355.5	none	negative

*Reduction in mitotic index of ≥ 50%.

Remarks - Results

Under all experimental conditions, there was no evidence of an increase in the proportion of cells with chromosomal aberrations. No statistically

	significant increases in polyploidy metaphases were observed. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human peripheral blood lymphocytes cells treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm (2010d)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310 Ready Biodegradability: CO_2 in Sealed Vessel Test
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Analysed for Total Organic Carbon (TOC) using a Shimadzu TOC-V-CPH Carbon analyser
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Notified chemical		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	26.2	4	85.6
7	60.3	7	93.3
28	83.5	28	97.0

Remarks - Results

All validity criteria for the test were satisfied. The reference compound, sodium benzoate, achieved > 85% degradation by Day 4, and therefore the test is considered valid for this criterion.

The toxicity control achieved 75.5% degradation by Day 14 and, as this surpasses the pass level of 25%. Therefore, the test material is considered non-inhibitory to the inoculum used in the study.

The degree of degradation of the notified chemical after the cultivation period was 83.5% and it reached the pass level within the 10-day window. Therefore, the test substance is classified as readily biodegradable according to the OECD (310) guideline.

CONCLUSION	The notified chemical is readily biodegradable
TEST FACILITY	Firmenich (2007)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Not reported
Water Hardness	250 mg $CaCo_3$/L
Analytical Monitoring	GC Analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

The highest treatment of 100 mg/L was prepared by completing dissolving the test substance in test water using intense stirring for 15 minutes at room temperature. The highest treatment was serially diluted with test

water to prepare the lower treatments.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Cumulative % Immobilised*	
Nominal	*Geometric mean measured*		*24 h*	*48 h*
Control	Control	20	0	0
0.32	Not analysed	20	0	0
1.0	Not analysed	20	0	0
3.2	Not analysed	20	0	0
10	8.0	20	0	0
32	26	20	15	45
100	84	20	55	100

EC50	27.0 (22.0 – 40.0) mg/L at 48 hours
NOEC	8.0 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The treatment concentrations were measured at the beginning and end of the test. The 48-hour EC50 was calculated based on the geometric mean measured concentrations of 0 and 48 hours, by Weibull analysis.

CONCLUSION The notified chemical is harmful to aquatic invertebrates

TEST FACILITY Harlan (2011a)

C.2.2. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0.32, 1.0, 3.2, 10, 32 and 100 mg/L Geometric mean measured: 0.15, 0.54, 1.8, 6.0, 21 and 88 mg/L
Auxiliary Solvent	Not reported
Water Hardness	24 mg $CaCo_3$/L
Analytical Monitoring	HPLC method
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. The highest treatment of 100 mg/L was prepared by completing dissolving the test substance in test water using ultrasonic treatment for 10 minutes and intense stirring for 15 minutes at room temperature. Then, the treatment was allowed to settle in a separating funnel for 30 minutes to separate undissolved test substance from the solution. The middle layer (clear phase) was used as the highest treatment. The highest treatment was serially diluted with test water to prepare the lower treatments.

RESULTS

Biomass (72 h)		*Growth (72 h)*	
E_yC50 (mg/L)	*NOE_yC (mg/L)*	*E_rC50 (mg/L)*	*NOE_rC (mg/L)*
11 (9.9 – 13)	0.9	25 (23 – 28)	0.9

Remarks - Results	All validity criteria for the test were satisfied. The end points were determined based on the geometric mean measured test concentrations. The treatments concentrations were measured at the beginning and end of the 72-h test period.
CONCLUSION	The notified chemical is harmful to algae
TEST FACILITY	Harlan (2011b)

C.2.3. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sludge
Exposure Period	3 minutes
Concentration Range	Nominal: 10, 32, 100, 320, and 1000 mg/L
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. Due to the volatile nature of the test substance, the test duration was reduced from 3 hours to 30 minutes. It was considered likely that a longer test duration would result in significant losses of test substance from the test system.
RESULTS	
EC20	Not reported
EC50	460 (370-570) mg/L
Remarks – Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified chemical inhibits microbial respiration
TEST FACILITY	Harlan (2010e)

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