LTD/1677

February 2015

**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)**

# PUBLIC REPORT

## Methyl Citral

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

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

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


| | |
|---|---|
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**Director**
**NICNAS**

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# SUMMARY

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

| ASSESSMENT REFERENCE | APPLICANT(S) | CHEMICAL OR TRADE NAME | HAZARDOUS CHEMICAL | INTRODUCTION VOLUME | USE |
|---|---|---|---|---|---|
| LTD/1677 | Firmenich Limited | Methyl Citral | Yes | < 1 tonne per annum | Fragrance ingredient in cosmetic and personal care/ household products |

# CONCLUSIONS AND REGULATORY OBLIGATIONS

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

| *Hazard classification* | *Hazard statement* |
|---|---|
| Eye irritation (Category 2A) | H319 - Causes serious eye irritation |
| Skin irritation (Category 2) | H315 – Causes skin irritation |
| Skin sensitisation (Category 1) | H317 - May cause an allergic skin reaction |

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

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 2 | H401 - Toxic to aquatic life |
| Chronic Category 2 | H411 - Harmful to aquatic life with long lasting effects |

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

When used at ≤ 0.19% in fine fragrances and ≤ 0.1% in cosmetic and personal care/household products, the notified chemical is not considered to pose an unreasonable risk to public health.

**Environmental risk assessment**

On the basis of the PEC/PNEC ratio and the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

**Recommendations**

REGULATORY CONTROLS
Hazard Classification and Labelling

- The notified chemical should be classified as follows:

- Eye irritation (Category 2A): H319 - Causes serious eye irritation
- Skin irritation (Category 2): H315 – Causes skin irritation
- Skin sensitisation (Category 1): H317 - May cause an allergic skin reaction

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

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following isolation and engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Coveralls, impervious gloves, goggles (during reformulation processes)
  - Impervious gloves (during application of end-use products)

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

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

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤0.19% in fine fragrances and ≤0.1% in other cosmetic and personal care/household products

Disposal

- Where re-use or recycling are unavailable or impracticable, dispose of the chemical in an environmentally sound manner in accordance with the relevant Commonwealth, State, Territory and local government legislation.

Emergency procedures

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

**Regulatory Obligations**

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 0.19% in fine fragrances or 0.1% in other cosmetic and personal care/household products.

or

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

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

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

# ASSESSMENT DETAILS

## 1. APPLICANT AND NOTIFICATION DETAILS

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

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

## 2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Methyl Citral

MOLECULAR WEIGHT
< 500 Da

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

## 3. COMPOSITION

DEGREE OF PURITY > 75%

## 4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

| Property | Value | Data Source/Justification |
|---|---|---|
| Melting Point/Freezing Point | < -20 ± 0.5 °C | Measured |
| Boiling Point | 241°C at 96.9 kPa | Measured |
| Density | 897 kg/m$^3$ at 20 ± 0.5 °C | Measured |
| Vapour Pressure | 3.3 x 10$^{-3}$ kPa at 25 °C | Measured. It is considered to be volatile based on this value. |
| Water Solubility | 0.352 g/L at 20 °C | Measured. The notified chemical is expected to be dispersible in water. |
| Hydrolysis as a Function of pH | Hydrolytically stable | Measured |
| Partition Coefficient (n-octanol/water) | log Pow = 3.06 | Measured |
| Surface Tension | 57.0 mN/m at 20.5 ± 0.5 °C | Measured |
| Adsorption/Desorption | log $K_{oc}$ = = 2.39 to 2.55 | Measured |
| Dissociation Constant | Not determined | Does not contain dissociable |

| | | |
|---|---|---|
| | | functionalities. |
| Flash Point | 112 ± 2 °C at 101.3 kPa (closed cup) | Measured |
| Autoignition Temperature | 266 ± 5 °C | Measured |
| Explosive Properties | Not determined | Not expected to be explosive based on structure |
| Oxidising Properties | Not determined | Not expected to be oxidising based on structure |

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

*Reactivity*
The notified chemical is shown to be stable under normal conditions of use (between pH 5 to 8.5).

***Physical hazard classification***
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

## 5. INTRODUCTION AND USE INFORMATION

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

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

USE
The notified chemical is intended to be used as a component of fragrances for a variety of cosmetic and personal care/household products (proposed usage concentration: ≤1% in fine fragrances and ≤0.1% in cosmetic and personal care/household products).

OPERATION DESCRIPTION
The procedures for incorporating the imported fragrance preparations (containing ≤ 5% notified chemical) into end-use products will likely vary depending on the nature of the cosmetic and personal care/household products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation process will involve blending operations that will be highly automated and occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes.

The finished products containing the notified chemical may be used by consumers and professionals such as hairdressers, workers in beauty salons and cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

## 6. HUMAN HEALTH IMPLICATIONS

### 6.1. Exposure Assessment

#### 6.1.1. Occupational Exposure

CATEGORY OF WORKERS

| *Category of Worker* | *Exposure Duration (hours/day)* | *Exposure Frequency (days/year)* |
|---|---|---|
| Transport | Unknown | Unknown |
| Mixer | 4 | 2 |
| Drum handling | 4 | 2 |
| Drum cleaning | 4 | 2 |
| Maintenance | 4 | 2 |
| Quality control | 0.5 | 1 |
| Packaging | 4 | 2 |
| Salon workers | Unspecified | Unspecified |
| Cleaners | Unspecified | Unspecified |

EXPOSURE DETAILS
Transport and storage workers may come in contact with the notified chemical as a component of the imported fragrance preparations (≤ 5% concentration) or end-use products (≤ 1% concentration), only in the event of rupture of containers.

During reformulation, dermal, ocular and inhalation exposure of workers to the notified chemical (at ≤5% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of the equipment. Exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems as well as 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 ≤ 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to the clients (e.g. hair dressers, workers in beauty salons) or in the cleaning industry. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of similar or lesser extent than that experienced by consumers using products containing the notified chemical.

#### 6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤1% concentration) through the use of household products and rinse-off and leave-on cosmetic and personal care products. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2010; Cadby *et al.*, 2002; SDA, 2005). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, the default dermal absorption of 100% is assumed for calculation purposes (European Commission, 2003). For the inhalation exposure assessment (European Commission, 2003; SDA, 2005), an adult inhalation rate of 23 $m^3$/day (enHealth, 2004) is used and it is assumed that the bioavailability of the notified chemical via the inhalation route is 100%. An adult bodyweight of 60 kg is used for calculation purposes.

Based on the above information, the daily systemic exposure to the notified chemical through the use of the cosmetic and household products is estimated as following:

| Product type | Daily systemic exposure (mg/kg bw/day) |
|---|---|
| *Cosmetic products (dermal exposure)* | |
| Body lotion | 0.130 |
| Face cream | 0.026 |
| Hand cream | 0.036 |
| Fine fragrances | 0.125 |
| Deodorant spray | 0.024 |
| Shampoo | 0.002 |
| Conditioner | 0.001 |
| Shower gel | 0.003 |
| Hand soap | 0.003 |
| Hair styling products | 0.007 |
| **Subtotal** | **0.356** |
| *Household products (dermal exposure from wearing clothes)* | |
| Laundry liquid | 0.004 |
| Fabric softener | 0.001 |
| **Subtotal** | **0.005** |
| *Household products (direct dermal exposure)* | |
| Laundry liquid | 0.00003 |
| Dishwashing liquid | 0.00027 |
| All-purpose cleaner | 0.0023 |
| **Subtotal** | **0.0026** |
| *Cosmetic products (inhalation exposure)* | |
| Hairspray | 0.040 |
| **Subtotal** | **0.040** |
| **Total** | **0.4036** |

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 0.4 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, in particular assuming an airspace volume of 2 $m^3$, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners).

### 6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the 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 |
| Rat, acute dermal toxicity | LD50 > 2000 mg/kg bw |
| Rabbit, skin irritation | slightly irritating |
| Rabbit, eye irritation | irritating |
| Mouse, skin sensitisation – Local lymph node assay | evidence of sensitisation |
| Human, skin sensitisation – Repeat insult patch test (1%) | no evidence of sensitisation |
| Rat, repeated dose oral toxicity – 28 days. | NOAEL = 750 mg/kg bw/day |
| Mutagenicity – bacterial reverse mutation | non mutagenic |
| Genotoxicity – in vitro human lymphocytes | non genotoxic |

*Toxicokinetics, metabolism and distribution.*
Based on the low molecular weight (< 500), moderate water solubility (0.352 g/L at 20 °C) and partition coefficient (log Pow = 3.06), absorption across biological membranes including skin, GI tract and lungs is expected. While the notified chemical's surfactant properties may also contribute to the dermal absorption potential, the chemical is also moderately volatile indicating that some of the applied dose may be lost to air.

*Acute toxicity.*
The notified chemical was found to be of low acute dermal ($LD_{50}$ > 2000 mg/kg bw) and oral ($LD_{50}$ > 2000 mg/kg bw) toxicity in the rat.

However in the rat acute dermal study (Wistar strain), signs of systemic toxicity were observed in the form of red/brown staining around the snout in 4/5 males and 2/5 females. All animals displayed slight to well-defined erythema and other signs of dermal irritation. Most of these signs disappeared at days 10-12 except in three females where superficial scabs persisted until day 14.

*Irritation*
The notified chemical was irritating to rabbit skin and irritating to the rabbit eye.

In an acute eye irritation study using a single application of the notified chemical to the non-irrigated eye of three New Zealand white rabbits, scattered or diffuse corneal opacity and moderate conjunctival irritation were observed. In one animal, alopecia around the treated eye was observed. One treated eye appeared normal at day 7 and the other two at day 14. The scores warranted classification of the chemical as an eye irritant under the GHS, however the scores did not warrant classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

In an acute dermal irritation study using three New Zealand white rabbits, a 3-minute and 1-hour semi-occluded applications of the notified chemical to the intact skin of one rabbit produced no corrosive effects. In two rabbits, a single 4-hour, semi-occluded application of the notified chemical resulted in well-defined erythema and slight or moderate oedema. Other skin reactions were also noted including slight or moderate desquamation at both treated skin sites at day 14. The results of the study warranted classification of the notified chemical as a skin irritant.

There are no inhalation studies available on the notified chemical. It is volatile (vapour pressure = 3.3 x $10^{-3}$ kPa at 25 °C) therefore irritant effects through inhalation due to the notified chemical cannot be ruled out.

*Sensitisation.*
The notified chemical was a skin sensitiser in mice (Local Lymph Node Assay: stimulation indices of 1.18, 8.53 and 8.48 at 1, 10 and 100%, respectively). The $EC_3$ value was calculated to be 3.2%. The notified chemical was not a skin sensitiser at 1% concentration in a human repeat insult patch test (HRIPT).

*Repeated Dose Toxicity.*
A 28-day repeated dose study by oral gavage was conducted in Wistar strain rats. There were no unscheduled deaths during the study and no macroscopic abnormalities were detected at terminal kill. There was a statistically significant dose related decrease in the last 20% activity (a functional performance test) in the male treatment groups however the study authors did not find this of toxicological significance. A statistically significant decrease in body weight gain at week four was observed in males at the high dose. Statistically significant decreases in body weight gain at weeks one and three were observed in females at all treatment groups. A statistically significant decrease in pituitary weight was observed in males at the high treatment group and in females at all treatment groups. The study report does not find the decreased pituitary weights to be of toxicological significance.

A NOAEL of 750 mg/kg bw/day was derived by the study authors however a significant body of data on other similar citrals (NICNAS, 2013) over longer exposure periods indicate significant adverse effects at lower doses (100-200 mg/kg bw/day). Therefore, while a higher NOAEL has been derived from this short term repeated dose study, adverse effects (such as reduced body weight and hormonal imbalance from pituitary weight decrease) from a longer exposure period are possible.

*Mutagenicity*
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an in vitro mammalian chromosome aberration test.

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

| *Hazard classification* | *Hazard statement* |
|---|---|
| Eye irritation (Category 2A) | H319 - Causes serious eye irritation |
| Skin irritation (Category 2) | H315 – Causes skin irritation |
| Skin sensitisation (Category 1) | H317 - May cause an allergic skin reaction |

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R38: Irritating to skin
R43: May cause sensitisation by skin contact

### 6.3. Human Health Risk Characterisation

#### 6.3.1. Occupational Health and Safety

*Reformulation*
Exposure of workers to the notified chemical (at ≤ 5% concentration) may occur during blending operations. Ingestion is unlikely under the occupational settings described. The notified chemical is considered to be a skin and eye irritant and skin sensitiser. In addition, harmful effects following inhalation exposure to the notified chemical cannot be ruled out. Hence, caution should be exercised when handling the notified chemical during reformulation processes.

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

*End-use*
Cleaners and beauty care professionals will handle the notified chemical at ≤1% concentration, similar to public use. Therefore, the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

#### 6.3.2. Public Health

Members of the public may experience repeated exposure to the notified chemical (at ≤ 1% concentration) through the use of fine fragrances and personal and household products.

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.4 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 750 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on the notified chemical. A MoE value ≥ 300 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure. Using the abovementioned NOAEL, a MoE of 1857 was estimated, which is considered to be acceptable.

The notified chemical causes skin irritation and serious eye irritation. Skin irritation effects are not expected from use of the notified chemical at the revised (lowered) concentrations. The potential for eye irritation would be reduced at the low concentrations of use, however the potential for eye irritation cannot be ruled out.

Ocular exposure is only expected to occur in the event of an accident, and, in the case of household products, the products may be diluted with water at the time of eye contact.

The notified chemical is considered to have the potential to cause skin sensitisation. Methods for the quantitative risk assessment of dermal sensitisation have been proposed and been the subject of significant discussion (see for

example, Api *et al.*, 2008 and RIVM, 2010). Using a fine fragrance (containing 1.0 % notified chemical) as an example product that may contain the notified chemical, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 37.5 μg/cm$^2$ (Cadby *et al.*, 2002).

When tested in an LLNA study, the notified chemical was a skin sensitiser with an $EC_3$ value of 3.2%. Although this value has been used for the purposes of a quantitative risk assessment of the notified chemical given the standard protocol in the LLNA study, the availability of additional information on the sensitisation potential of the notified chemical (i.e. a negative HRIPT when tested at 1% concentration) was taken into account when determining the safety assessment factors that should be applied. This allowed for the derivation of an Acceptable Exposure Level (AEL) = 7.18 μg/cm$^2$. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of approximately 100 (100 used for calculations).

As the AEL<CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances at 1.0% concentration is considered to be unreasonable. An AEL equivalent to the CEL may be attained from reducing concentrations of the notified chemical in fine fragrances to ≤ 0.19% notified chemical. For other cosmetic products, using face cream as a worst case exposure assumption, for a proposed use concentration of 0.1% the AEL>CEL. Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.19% in fine fragrances and ≤ 0.1% in cosmetic and personal care/household products, is not considered to be unreasonable.

## 7. ENVIRONMENTAL IMPLICATIONS

### 7.1. Environmental Exposure & Fate Assessment

#### 7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as a component of perfume preparations. Environmental release of the notified chemical during importation, storage and transportation is not expected except in the event of accidental spills or leaks. Spills or leaks from drums are expected to be collected with inert material and disposed of to landfill.

Release of the notified chemical to the environment during blending of the cosmetic and household products is not expected to be significant. Potential sources of release include spills, equipment washing, and container residues. A total of 0.1% of waste may be generated as a result of spills. It is expected that blending equipment will be cleaned using water and the aqueous solution reused. Therefore, no significant release is anticipated from cleaning of the formulation equipment. The average amount of residue in empty containers is estimated to be < 0.1%. Therefore a total of 0.2% or up to 2 kg of waste notified chemical is expected to be generated each year from the formulation process.

Empty import containers containing the notified chemical are expected to either be recycled or be disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

As a component of consumer products (cosmetics, toiletries, household products), most of the notified chemical is expected to be released to sewer after use.

RELEASE OF CHEMICAL FROM DISPOSAL

The end-use empty containers, estimated to contain < 3% of the annual import volume of the notified chemical, are expected to be disposed of to landfill or sent for recycling. Residues of the notified chemical in the empty import containers may also be thermally decomposed during the recycling of the empty drums.

#### 7.1.2. Environmental Fate

The notified chemical is not considered readily biodegradable. However, it is not expected to be persistent in the environment (biodegradability of about 60% in 28 days). For the details of the environmental fate studies please refer to Appendix C.

Most of the notified chemical is expected to be released to sewer after use. A small amount of the notified chemical may be disposed of to landfill as residues in empty product containers. Residues of the notified chemical may also be thermally decomposed during recycling of the empty import containers, forming water and oxides of carbon. In sewage treatment plants (STPs), part of the notified chemical is expected to sorb to sludge based on the n-octanol/water partition coefficient (log $P_{OW}$ = 3.06). The sludge containing notified chemical residues may be sent to landfill or applied to soils for land remediation. A proportion of the notified chemical may also be discharged in treated effluent to receiving waters where the chemical is expected to disperse and degrade. As a hydrophobic organic chemical having low molecular weight of below 500 Da, the notified chemical has the potential to bioaccumulate in aquatic organisms. However, the reported biodegradability, volatility, and the expected adsorption to sludge sediment decrease the bioaccumulation potential of the notified chemical. In water or landfill, the notified chemical is expected to ultimately degrade biotically and abiotically to form water and oxides of carbon.

The notified chemical is expected to be volatile and may volatilise to air during use or STP processes. The half-life of the notified chemical in air is calculated to be 0.8 hours based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

### 7.1.3. Predicted Environmental Concentration (PEC)

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

| ***Predicted Environmental Concentration (PEC) for the Aquatic Compartment*** | | |
|---|---|---|
| Total Annual Import/Manufactured Volume | 1,000 | kg/year |
| Proportion expected to be released to sewer | 100% | |
| Annual quantity of chemical released to sewer | 1,000 | kg/year |
| Days per year where release occurs | 365 | days/year |
| Daily chemical release: | 2.74 | kg/day |
| Water use | 200 | 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. However, these are likely to be maximum values given the potential for the notified chemical to volatise into the air compartment.

## 7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

| *Endpoint* | *Result* | *Assessment Conclusion* |
|---|---|---|
| Fish Toxicity | 96 h EC50 = 3.11 mg/L | Toxic to fish |

| | | |
|---|---|---|
| Daphnia Toxicity | 48 h EC50 = 2.3 mg/L | Toxic to aquatic invertebrates |
| Algal Toxicity | 72 h EC50 = 1.5 mg/L<br>72 h NOEC = 0.46 mg/L | Toxic to algae |
| Inhibition of Bacterial Respiration | 3 h EC50 = 140 mg/L | Not expected to be inhibitory to microbial activity |

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is considered to be acutely toxic to fish, aquatic invertebrates, and algae, but not harmful to sludge bacteria. Based on the toxicity to aquatic biota the notified chemical is formally classified under the GHS as "Acute category 2; Toxic to aquatic life". Based on the NOEC for algal NOEC and the acute effects to the three trophical levels, the notified chemical is formally classified as "Chronic category 2; Toxic to aquatic life with long lasting effects" under the GHS.

### 7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) has been calculated using the most sensitive endpoint for algae. A safety factor of 100 was used given endpoints for three trophic levels are available.

| ***Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment*** | | |
|---|---|---|
| $E_rC50$ (Algae, 72 h) | 1.5 | mg/L |
| Assessment Factor | 100 | |
| PNEC: | 15 | µg/L |

### 7.3. Environmental Risk Assessment

The Risk Quotient (PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

| Risk Assessment | PEC µg/L | PNEC µg/L | Q |
|---|---|---|---|
| Q - River | 0.61 | 15 | 0.04 |
| Q - Ocean | 0.06 | 15 | 0.004 |

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. The notified chemical is expected to have a low potential for bioaccumulation. Therefore, on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

## APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

**Melting Point/Freezing Point** < -20.0 ± 0.5 °C

| | |
|---|---|
| Method | OECD TG 102 Melting Point/Melting Range.<br>EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature. |
| Remarks | Determined by placing a test tube containing the test substance in a dry ice/isopropanol bath until the temperature of the test substance reached approximately -20.0 °C. The test substance did not show any indication of freezing. |
| Test Facility | Firmenich (2010) |

**Boiling Point** 241 °C at 96.9 kPa

| | |
|---|---|
| Method | OECD TG 103 Boiling Point.<br>EC Council Regulation No 440/2008 A.2 Boiling Temperature. |
| Remarks | Determined according to the Siwoloboff method. |
| Test Facility | Firmenich (2010) |

**Density** 897 kg/$m^3$ at 20 ± 0.5 °C

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

**Vapour Pressure** 3.3 x $10^{-3}$ kPa at 25 °C

| | |
|---|---|
| Method | OECD TG 104 Vapour Pressure.<br>EC Council Regulation 761/2009 amending Regulation No 440/2008 A.4 Vapour Pressure. |
| Remarks | Determined using the gas saturation method. The experiments were performed at -1°C, 10°C and 20 °C. The vapour pressure of the notified chemical at 25 °C was calculated to be 3.3 x $10^{-3}$ kPa by extrapolation from the vapour pressure curve (1.9 x $10^{-4}$ kPa at -1°C, 6.5 $10^{-4}$ kPa at 10 °C, and 2.1 x $10^{-3}$ kPa at 20 °C. |
| Test Facility | Harlan (2011j) |

**Water Solubility** 0.352 g/L at 20 °C

| | |
|---|---|
| Method | OECD TG 105 Water Solubility.<br>EC Council Regulation No 440/2008 A.6 Water Solubility. |
| Remarks | Flask Method was used following a preliminary assessment of the water solubility using the WSKOW model (EPISuite, USEPA, 2011). Mixtures of the notified chemical and water at approximately 4 g/L were prepared in three replicates and shaken for 8 hours at 30°C, followed by standing at 20°C for 24 hours. Aqueous solutions were then taken and filtered (45 µm filter) for HPLC analysis to determine the water solubility. The water solubility was determined to be 0.352 g/L at 20 °C. |
| Test Facility | Firmenich (2010) |

**Hydrolysis as a Function of pH** Hydrolytically stable at pH 5-8.5

Method Test guideline not provided.

| *pH* | *T (°C)* | *Test Substance Remaining at Day 28 (%)* |
|---|---|---|
| 2 | 40 | < LOD* |
| 5 | 40 | 60 |
| 7 | 40 | 87 |
| 8.5 | 40 | 80 |
| 12 | 40 | <LOD |

* LOD: Limit of detection.

| | |
|---|---|
| Remarks | The stability of the notified chemical was determined at pH values ranging from 2 – 12 under accelerated conditions of 40 °C for 28 days. The initial concentration of the notified chemical was 200 – 300 ppm. GC was used for determination of the concentrations. Results indicated that no test substance could be detected at pH 2 and 12 after 8 days of the experiment. The notified chemical remaining after day 28 of the test was determined to be approximately 60%, 87% and 80% of the initial concentration at pH 5, 7, and 8.5, respectively. The results suggest that the notified chemical is hydrolytically stable in the pH range of 5 – 8.5. |
| Test Facility | Firmenich (undated) |

**Partition Coefficient (n-octanol/water)** log Pow = 3.06

| | |
|---|---|
| Method | OECD TG 117 Partition Coefficient (n-octanol/water).<br>EC Council Regulation No 440/2008 A.8 Partition Coefficient. |
| Remarks | HPLC Method was used using a column temperature of 30 °C and a mobile phase pH value of 6. The dead time was determined to be 3.73 minutes. Two peaks were detected with a mean retention time of 10.87 minutes. The log Pow was calculated as 3.06 for the notified chemical. |
| Test Facility | Firmenich (2010) |

**Surface Tension** 57.0 mN/m at 20.5 ± 0.5 °C

| | |
|---|---|
| Method | OECD TG 115 Surface Tension of Aqueous Solutions.<br>EC Council Regulation No 440/2008 A.5 Surface Tension. |
| Remarks | Concentration: 0.21 g/L<br>Determined using the ring method. The test item is considered surface-active (based on the OECD and EC methods) but not significantly (based on the chemical structure and emulsification potential in n-octanol and water). |
| Test Facility | Harlan (2011i) |

**Adsorption/Desorption – main test** log $K_{oc}$ = 2.39 to 2.55

| | |
|---|---|
| Method | OECD TG 121 Estimation of the Adsorption Coefficient (Koc ) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC). |
| Remarks | HPLC screening method was used using a column temperature of 40 °C and a mobile phase of methanol/water (55/45 v/v). The dead time was determined to be 1.956 minutes (formamide). Two peaks were detected with a retention time of 2.39 and 2.55 minutes. The log $K_{OC}$ was calculated in the range of 2.39 to 2.55 for the notified chemical. |
| Test Facility | Harlan (2011g) |

# APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

## B.1. Acute toxicity – oral

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.<br>EC Council Regulation No 440/2008 B.1 bis Acute toxicity (oral) fixed dose method. |
| Species/Strain | Rat/Wistar |
| Vehicle | Arachis Oil BP |
| Remarks – Method | No significant protocol deviations. |

RESULTS

| *Group* | *Number and Sex of Animals* | *Dose mg/kg bw* | *Mortality* |
|---|---|---|---|
| 1 | 1F | 300 | 0/1 |
| 2 | 5F | 2000 | 0/5 |

| | |
|---|---|
| LD50 | >2000 mg/kg bw |
| Signs of Toxicity | No signs of systemic toxicity were noted. |
| Effects in Organs | No abnormalities in individual necropsy findings were observed. |
| Remarks – Results | All animals showed expected gains in body weight during the study except for one animal treated at 2000 mg/kg which showed no gain in body weight during the first week but expected gain in body weight during the second week. |
| CONCLUSION | The notified chemical is of low toxicity via the oral route. |
| TEST FACILITY | Harlan (2011d) |

## B.2. Acute toxicity – dermal

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 402 Acute Dermal Toxicity – Limit Test.<br>EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test. |
| Species/Strain | Rat/Wistar |
| Vehicle | Arachis Oil BP |
| Type of dressing | Semi-occlusive |
| Remarks - Method | No significant protocol deviations. |

RESULTS

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

| | |
|---|---|
| LD50 | >2000 mg/kg bw |
| Signs of Toxicity - Local | Red/brown staining around the snout was noted in four males and two females during the day of dosing. |
| Signs of Toxicity - Systemic | None |
| Effects in Organs | None |
| CONCLUSION | The notified chemical is of low toxicity via the dermal route. |
| TEST FACILITY | Harlan (2011b) |

### B.3. Irritation – skin

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 404 Acute Dermal Irritation/Corrosion.<br>EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation). |
| Species/Strain | Rabbit/New Zealand White |
| Number of Animals | 2 M |
| Vehicle | None |
| Observation Period | 14 days |
| Type of Dressing | Semi-occlusive |
| Remarks - Method | For the first rabbit three sites were treated with 0.5 mL of the undiluted test substance. The sites were evaluated at 3 minutes, 1 hour and 4 hours. A second rabbit was treated with 0.5 mL of the test substance at a single site for 4 hours. |

RESULTS

| *Lesion* | *Mean Score* Animal No.* | | *Maximum Value* | *Maximum Duration of Any Effect* | *Maximum Value at End of Observation Period* |
|---|---|---|---|---|---|
| | 1 | 2 | | | |
| *Erythema/Eschar* | 2.0 | 2.0 | 2.0 | <14 days | 0 |
| *Oedema* | 2.0 | 2.0 | 2.0 | <14 days | 0 |

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

| | |
|---|---|
| Remarks - Results | The pH of the undiluted test substance was 3.3<br><br>*3 minute exposure period*<br>Well-defined erythema and very slight oedema were noted at 21, 48 and 72 hr. Moderate desquamation was noted 7 and 14 days.<br><br>*1 hour exposure period*<br>Very slight erythema was noted at 24, 48 and 72 hr. Moderate desquamation was noted 7 and 14 days.<br><br>*4 hour exposure period*<br>Well-defined erythema and slight or moderate oedema were noted at 1 hr and well-defined erythema and slight oedema at 24, 48 and 72 hr. Very slight erythema was noted at 7 days. Other observations between day 1 and day 14 include blanching, light brown discolouration of the epidermis, loss of skin elasticity, crust formation and slight to moderate desquamation. At the 14 day observation, moderate desquamation was noted at one treated skin site and slight desquamation was noted at the other. |
| CONCLUSION | The notified chemical is irritating to skin. |
| TEST FACILITY | Harlan (2011a) |

### B.4. Irritation – eye

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 405 Acute Eye Irritation/Corrosion.<br>EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation). |
| Species/Strain | Rabbit/New Zealand White |
| Number of Animals | 3 M |
| Observation Period | 14 days |
| Remarks - Method | This test was performed to confirm the initial assessment, a Rabbit Enucleated Eye test (REET) which gave borderline positive result. |

RESULTS

| *Lesion* | *Mean Score* Animal No.* | | | *Maximum Value* | *Maximum Duration of Any Effect* | *Maximum Value at End of Observation Period* |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | | |
| *Conjunctiva: redness* | 1.7 | 2.0 | 2.0 | 2.0 | 7 days | 0.0 |
| *Conjunctiva: chemosis* | 1.7 | 1.0 | 1.3 | 2.0 | 7 days | 0.0 |
| *Conjunctiva: discharge* | 1.0 | 0.7 | 1.3 | 2.0 | 72 hr | 0.0 |
| *Corneal opacity* | 0.7 | 1.0 | 1.0 | 1.0 | 72 hr | 0.0 |
| *Iridial inflammation* | 0.0 | 0.0 | 0.0 | 0.0 | - | 0.0 |

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

Remarks - Results

Scattered or diffuse corneal opacity was noted in two treated eyes at 1 and 24 hr. Moderate conjunctival irritation was noted in two treated eyes with minimal conjunctival irritation in one treated eye at 48 and 72 hr. Minimal conjunctival irritation was noted in two treated eyes at 7 days. Alopecia around the treated eyes was noted in one animal at 7 days.
One treated eye appeared normal at 7 days and two treated eyes appeared normal at 14 days.

CONCLUSION

The notified chemical is irritating to the eye.

TEST FACILITY

Harlan (2011c)

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

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay.
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay).

Species/Strain: Mouse/CBA Ca

Vehicle: Acetone/olive oil (4:1)

Remarks - Method: A preliminary screening test was conducted using one mouse treated with 25 µL of undiluted test substance. A concurrent positive control was not conducted but recent positive control studies conducted by the laboratory demonstrated the sensitivity of the laboratory. There were no significant protocol deviations.

RESULTS

| *Concentration (% w/w)* | *Proliferative response (DPM/lymph node)* | *Stimulation Index (Test/Control Ratio)* |
|---|---|---|
| *Test Substance* | | |
| 0 (vehicle control) | 1789 | - |
| 1 | 2104 | 1.18 |
| 10 | 15268** | 8.53 |
| 100 | 15169* | 8.48 |

Remarks - Results

In the preliminary study, there were no signs of systemic toxicity or excessive irritation (the latter is indicated by ≥25% increase in mean ear thickness) noted. Very slight erythema was noted on both ears at days 1 to 4. No visual local skin irritation was noted at days 5 and 6.

In the main study, there were no deaths or signs of systemic toxicity observed in the test or control animals. Very slight erythema was noted on both ears of animals treated with the undiluted test substance and at

| | |
|---|---|
| | 10% concentration. No excessive irritation was noted. |
| CONCLUSION | There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical. |
| TEST FACILITY | Harlan (2011k) |

**B.6. Skin sensitisation – human volunteers**

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical (applied at 1% concentration) |
| METHOD | Human repeated insult patch test with challenge |
| Study Design | Induction Procedure: 9 induction applications made three times a week for three consecutive weeks. Skin was assessed 24 hours after patch removal (or 48 hours for weekend patches).<br>Rest Period: Approximately 2 weeks.<br>Challenge Procedure: 1 challenge application to a virgin site, followed by skin assessment 24, 48, 72 and 96 hours after application. |
| Study Group | 108 (72 F, 36 M) ranging in age from 18-78 years. |
| Vehicle | Not disclosed in the study report |
| Remarks - Method | Occlusive webril/adhesive patches (25 mm Hill Top Chamber System) containing 0.3 mL of test substance (that had been allowed to volatilise for 15-40 minutes), were held in place for 24 hours before removal by the applicants. Of the 120 enrolled subjects, ten subjects voluntarily withdrew due to personal reasons, one withdrew due to pregnancy, one discontinued due to protocol violation. No subject discontinued due to test material reaction. |
| RESULTS | |
| Remarks - Results | Scores of zero were noted 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 | HRL (2014) |

**B.7. Repeated dose toxicity**

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.<br>EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral). |
| Species/Strain | Rat/Wistar [Han: HsdHan: WIST] |
| Route of Administration | Oral – gavage |
| Exposure Information | Total exposure days: 28 days<br>Dose regimen: 7 days per week<br>Post-exposure observation period: None (culled at day 29) |
| Vehicle | Arachis Oil BP |
| Remarks - Method | No significant protocol deviations. |

RESULTS

| *Group* | *Number and Sex of Animals* | *Dose mg/kg bw/day* | *Mortality* |
|---|---|---|---|
| control | 5M + 5F | 0 | 0/10 |
| low dose | 5M + 5F | 30 | 0/10 |
| mid dose | 5M + 5F | 300 | 0/10 |
| high dose | 5M + 5F | 750 | 0/10 |

*Mortality and Time to Death*

There were no unscheduled deaths.

*Clinical Observations*

Episodes of increased salivation were observed in both sexes at 750 and 300 mg/kg bw/day.

*Behavioural, Functional and Sensory Observations*

There were no treatment-related changes in the behavioural assessment measurements.

A statistically significant and dose dependent reduction in the last 20% activity (known as the asymptotic period) was evident in males in all treatment groups (↓49% for low dose; ↓86% for mid dose; and ↓88% for high dose), but was not observed in females.

There were no treatment-related changes in sensory reactivity.

*Body Weights, Food Consumption and Water Consumption*

There was a reduction in body weight gain in males at 750 mg/kg bw/day compared to controls at week 3 (not statistically significant) and week 4 (statistically significant). Females in all treatment groups had statistically significant reductions in body weight at weeks 1 and 3. However, there was no clear dose response and no statistically significant differences between absolute body weight gain over the 4 week study period. It is unknown what effect longer term exposure may have on absolute body weight, noting that longer term exposure to similar citrals result in significant decreases in body weight (NICNAS, 2013).

There were no statistically significant differences in either mean weekly food consumption or food efficiency in either sex at any dose group, although a non-statistically significant trend in reduction in food efficiency in males at 750 mg/kg bw/day at weeks 3 and 4 and in females from all treatment groups during weeks 1 and 3 was noted.

*Laboratory Findings – Haematology and Blood Chemistry*

In male rats treated at 750 and at 300 mg/kg bw/day, statistically significant (but not dose related) findings were noted on the following: increased total erythrocyte counts, reduced activated partial thromboplastin time and increased haematocrit levels. Males at 750 mg/kg bw/day also had a statistically significant reduction in mean corpuscular haemoglobin levels. No dose related and statistically significant responses were seen in females.

In female rats statistically significant and dose related reduction in total protein levels were seen from all treatment groups and in albumin levels at 750 and 300 mg/kg bw/day. The statistically significant reduction in alanine aminotransferase levels in females at 300 and 30 mg/kg bw/day did not show a dose related response. The only statistically significant (with no dose response) effect noted in the males was an increase in creatinine levels at 750 and 300 mg/kg bw/day.

While some effects were noted in both sexes the changes either showed no dose response, were within historical ranges or had no corresponding histopathological findings and were therefore considered by the study authors to be of no toxicological significance.

*Effects in Organs*

In male rats, statistically significant increases in liver weights (absolute and relative to terminal body weight) were seen at 750 and 300 mg/kg bw/day and at 750 mg/kg bw/day in females. There was also statistical significance in the decreased kidney weights (absolute and relative to terminal body weight) of males seen at 750 mg/kg bw/day.

A statistically significant dose related decrease in pituitary weights (absolute and relative to terminal body weight) was noted in females from all treatment groups and in males treated at 750 mg/kg bw/day.

However, the study authors determined these organ effects to be of no toxicological significance in the absence of any histopathological abnormalities, or due to adaptive effects as indicated for liver weight increase. It is noted that histopathological abnormalities, particularly in the pituitary may take longer than 28 days to eventuate.

*Necropsy and Histopathology*

There were no macroscopic abnormalities detected. The increased incidence and severity of centrilobular

hepatocellular hypertrophy observed in males at 750 mg/kg bw/day was attributed to the adaptive mechanism in rodent livers following the administration of xenobiotics. However, over a longer term study, exposure can induce centrilobular necrosis as noted in similar citrals (NICNAS, 2013). The exacerbation of hyaline droplets observed in the kidneys of males at 750 mg/kg bw/day is consistent with alpha-2-immunoglobulin excess which is an effect not relevant to humans. The increased incidence of kidney tubular basophilia observed in the kidneys of males at 750 mg/kg bw/day was not considered to be an adverse reaction as it is reversible.

Remarks – Results

The study authors did not find the decreased pituitary weights to be of toxicological significance. However, in the absence of further information and the trends towards decreased body weight, the significance of the effect is unknown. Endocrine disrupting chemicals are known to take longer periods to induce downstream effects (hormone imbalance) caused by pituitary decline. Other similar citrals (NICNAS, 2013) show significant decreases in sperm cells and testis weights over longer exposure periods with NOAELs of ~200 mg/kg bw/day. Therefore, while a NOAEL of 750 mg/kg bw/day is derived, there is significant uncertainty surrounding repeated dose effects over longer periods of time (e.g. 90 days).

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 750 mg/kg bw/day by the study authors in this study, based on absence of significant adverse effects at lower dose levels.

TEST FACILITY Harlan (2011m)

### B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure/Pre incubation procedure

| | |
|---|---|
| Species/Strain | *S. typhimurium*: TA1535, TA1537, TA98 and TA100<br>*E. coli*: WP2uvrA |
| Metabolic Activation System | S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver |
| Concentration Range in Main Test | a) With metabolic activation: 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate<br>b) Without metabolic activation: 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate |
| Vehicle | Dimethyl sulfoxide |
| Remarks - Method | A range finding test was conducted using TA100 and WP2uvrA with and without metabolic activation between 0.15 – 5000 µg/plate. The range finding test was conducted using plate incorporation method. The main study was conducted using pre-incubation method with the *E. coli* strain concentrations starting from 5 µg/plate and the *S. typhimurium* strains tested up to 1500 µg/plate. The positive and untreated controls were dosed using plate incorporation method. |

RESULTS

| *Metabolic Activation* | *Test Substance Concentration (µg/plate) Resulting in:* | | | |
|---|---|---|---|---|
| | *Cytotoxicity in Preliminary Test* | *Cytotoxicity in Main Test* | *Precipitation* | *Genotoxic Effect* |
| *Absent* | | | | |
| Test 1 | ≥150 | ≥1500 | >5000 | negative |
| Test 2 | | ≥500 | >5000 | negative |
| *Present* | | | | |
| Test 1 | ≥150 | ≥1500 | >5000 | negative |
| Test 2 | | ≥1500 | >5000 | negative |

Remarks - Results A small statistically significant increase in TA100 revertant colony frequency was observed in the absence of metabolic activation at 150

µg/plate. This was considered to be of no biological significance due to the lack of a dose-response relationship and reproducibility. The positive controls produced satisfactory responses, thus confirming the sensitivity of the study.

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

TEST FACILITY Harlan (2011l)

**B.9. Genotoxicity – in vitro**

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line Human lymphocytes
Metabolic Activation System S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Vehicle Dimethyl sulfoxide

Remarks - Method A range finding study was conducted with and without metabolic activation at concentrations up to 1663 µg/mL.

| *Metabolic Activation* | *Test Substance Concentration (µg/mL)* | *Exposure Period* | *Harvest Time* |
|---|---|---|---|
| *Absent* | | | |
| Test 1 | 2.5, 5, 10*, 15*, 20*,40* and MMC* | 4 | 20 |
| Test 2 | 3.125, 6.25*, 12.5*, 25*, 37.5, 50 and CP8 | 24 | 0 |
| *Present* | | | |
| Test 1 | 5, 10*, 20*, 40*, 80*, 120 and MMC* | 4 | 20 |
| Test 2 | 6.25*, 12.5*, 25*, 50, 75, 100 and CP* | 4 | 20 |

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

RESULTS

| *Metabolic Activation* | *Test Substance Concentration (µg/mL) Resulting in:* | | | |
|---|---|---|---|---|
| | *Cytotoxicity in Preliminary Test* | *Cytotoxicity in Main Test* | *Precipitation* | *Genotoxic Effect* |
| *Absent* | | | | |
| Test 1 | ≥26 | ≥40 | not reported | negative |
| Test 2 | | ≥25 | not reported | negative |
| *Present* | | | | |
| Test 1 | ≥207.9 | ≥80 | not reported | negative |
| Test 2 | | ≥25 | not reported | negative |

Remarks - Results The test chemical did not induce a statistically significant increase in the frequency of cells with chromosomal aberrations in two separate tests with and without metabolic activation.

CONCLUSION The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY Harlan (2011f)

# APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

## C.1. Environmental Fate

### C.1.1. Ready biodegradability

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test. |
| Inoculum | Activated sewage sludge |
| Exposure Period | 28 days |
| Auxiliary Solvent | Not applied |
| Analytical Monitoring | BOD (biochemical oxygen demand) was determined, and its percentage over ThOD (theoretical oxygen demand) was used for the expression of biodegradability. |
| Remarks - Method | The study was conducted at nominal concentration of 100 mg/L in three replicates at 22± 1°C.<br>A control test, a standard test with sodium benzoate, an abiotic control test, and a toxicity control test were established.<br>The test was conducted according to test guideline (TG) using good laboratory practice (GLP). |

RESULTS

| *Notified chemical* | | *Sodium benzoate* | |
|---|---|---|---|
| *Day* | *% Degradation* | *Day* | *% Degradation* |
| 0 | 0 | 0 | 0 |
| 7 | 18 | 7 | 77 |
| 14 | 33 | 14 | 84 |
| 28 | 56 | 28 | 94 |

| | |
|---|---|
| Remarks - Results | All the test validity criteria were met.<br>The notified chemical was not toxic to the sludge bacteria since 61% degradation was achieved at Day 28. The notified chemical is not considered to be readily biodegradability since it failed to reach the degree of biodegradability of 60% at Day 28. However, it is not considered to be persistent due to the biodegradability of 56% reached. |
| CONCLUSION | The notified chemical is not readily biodegradable. However, it is not considered to be persistent. |
| TEST FACILITY | Firmenich (2011) |

### C.1.2. Ready biodegradability

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test. |
| Inoculum | Activated sewage sludge |
| Exposure Period | 28 days |
| Auxiliary Solvent | Not applied |
| Analytical Monitoring | BOD (biochemical oxygen demand) was determined, and its percentage over ThOD (theoretical oxygen demand) was used for expression of biodegradability. |
| Remarks - Method | The study was conducted at 93.6 mg/L in two replicates at 20± 0.5°C.<br>A control test, a reference test with sodium benzoate, and a toxicity control test were established.<br>The test was conducted according to test guideline (TG) using good laboratory practice (GLP). |

RESULTS

| *Notified chemical* | | *Sodium benzoate* | |
|---|---|---|---|
| *Day* | *% Degradation* | *Day* | *% Degradation* |
| 1 | 6.3 | 1 | 59.5 |

| | | | |
|---|---|---|---|
| 3 | 16.5 | 28 | 88.8 |
| 14 | 45.0 | | |
| 28 | 61.6 | | |

Remarks - Results

All the test validity criteria were met.
The notified chemical was not toxic to the sludge bacteria since 72.4% degradation was achieved at Day 28. The notified chemical reached the degree of biodegradability of >60% at Day 28. It is noted that the 10-day window criterion was not achieved. The study author argued that according to UNECE GHS (2011) Part 4: if the test substance is identified as a complex, multi-component substance with structurally similar constituents, the 10-day window condition may be waived. The notified chemical consists of two isomers having identical molecular formula, which are expected to have identical biodegradability. Therefore, the 10-day window condition is considered applicable for the notified chemical, and the notified chemical is not considered to be readily biodegradable.
It is not considered to be persistent due to the biodegradability of 61.6% reached at Day 28.

CONCLUSION

The notified chemical is not readily biodegradable. However, it is not considered to be persistent.

TEST FACILITY

Safety Evaluation Center (2012a)

## C.2. Ecotoxicological Investigations

### C.2.1. Acute toxicity to fish

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 203 Fish, Acute Toxicity Test – semi-static.
EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish - semi-static.

Species: Zebra fish (*Danio rerio*)
Exposure Period: 96 hours
Auxiliary Solvent: Not applied
Water Hardness: Not provided
Analytical Monitoring: The test concentrations were verified using reverse-phase HPLC method.
Remarks – Method:

Following a preliminary test, a definitive test was performed at nominal concentrations of 0.9, 1.4, 2.0, 2.9, and 4.3 µL/L. Two vessels were established at 23 ± 2°C for each treatment group with 10 fish used for each level. A blank control test was also performed in parallel. The test solution was renewed every 24 hours.

The 96 h LC50 was calculated based on the genomic mean concentrations in the fresh and expired solutions using EPA Trimmed Spearman-Kabber (TSK) method (version 1.5).

The test was conducted according to test guideline (TG) using good laboratory practice (GLP).

RESULTS

| *Concentration* | | *Number of Fish* | *Mortality** | | | |
|---|---|---|---|---|---|---|
| *Nominal (µL/L)* | *Actual (mg/L)* | | *24 h* | *48 h* | *72 h* | *96 h* |
| 0 | 0 | 10 | 0 | 0 | 0 | 0 |
| 0.9 | 0.797 | 10 | 0 | 0 | 0 | 0 |
| 1.4 | 1.19 | 10 | 0 | 0 | 0 | 0 |
| 2.0 | 1.71 | 10 | 0 | 0 | 0 | 0 |
| 2.9 | 2.46 | 10 | 0 | 0 | 0 | 0 |
| 4.3 | 3.92 | 10 | 8 | 10 | 10 | 10 |

* Sublethal effects were observed at all the test levels expected the lowest test level of 0.797 mg/L.

| | |
|---|---|
| LC50 | 3.11 mg/L (95% CL 2.46 – 3.92 mg/L) at 96 hours. |
| NOEC | 0.797 mg/L at 96 hours. |
| Remarks – Results | All test validity criteria were met.<br>The 96 h LC50 and NOEC were determined to be 3.11 mg/L (95% CL 2.46 – 3.92 mg/L) and 0.797 mg/L, respectively, based on the measured concentrations.<br>The notified chemical is considered to be toxic to fish based on the test results. |

CONCLUSION The notified chemical is toxic to fish based on the test results.

TEST FACILITY Safety Evaluation Center (2012b)

**C.2.2. Acute toxicity to aquatic invertebrates**

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test - static.
EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia - static.

| | |
|---|---|
| Species | *Daphnia magna* |
| Exposure Period | 48 hours |
| Auxiliary Solvent | Not applied |
| Water Hardness | 250 mg $CaCO_3$/L |
| Analytical Monitoring | The actual concentrations for the nominal levels 2.5 – 10 mg/L were analysed at start and end of the study by HPLC with UV/VIS detection. |
| Remarks - Method | Following a preliminary test, a definitive test was performed at nominal concentrations of 0.9, 1.4, 2.0, 2.9, and 4.3 µL/L. Two vessels were established at 23 ± 2°C for each treatment group with 10 fish used for each level. A blank control test was also performed in parallel. The test solution was renewed every 24 hours.<br>The 48 h EC50 was determined as the geometric mean values of the two consecutive test concentration with 0% (EC0) and 100% (EC100) immobility. The confidence limits correspond to the EC0 and EC100, respectively.<br>The test was conducted according to test guideline (TG) using good laboratory practice (GLP). |

RESULTS

| *Concentration mg/L* | | *Number of D. magna* | *Number Immobilised* | |
|---|---|---|---|---|
| *Nominal* | *Actual* | | *24 h* | *48 h* |
| 0 | --* | 20 | 0 | 0 |
| 0.63 | --* | 20 | 0 | 0 |
| 1.25 | --* | 20 | 0 | 0 |
| 2.5 | 1.6 | 20 | 0 | 0 |
| 5.0 | 3.4 | 20 | 4 | 20 |
| 10 | 7.0 | 20 | 20 | 20 |

* Actual concentration was not analysed since it is lower than the determined NOEC.

| | |
|---|---|
| EC50 | 2.3 mg/L at 48 hours (95% CL 1.6 – 3.4 mg/L) (geometric mean concentration) |
| NOEC | 1.6 mg/L at 48 hours |
| Remarks - Results | All the test validity criteria were met. During the test, a decrease of the test concentration in the test media occurred: 56% to 65% of the nominal concentration was detected at the end of the test. Therefore, the toxicity data were reported based on the geometric mean concentrations. |

| | |
|---|---|
| | The notified chemical is considered to be toxic to daphnia based on the reported test results. |
| CONCLUSION | The notified chemical is toxic to aquatic invertebrates |
| TEST FACILITY | Harlan (2011e) |

**C.2.3. Algal growth inhibition test**

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 201 Alga, Growth Inhibition Test.<br>EC Council Regulation No 440/2008 C.3 Algal Inhibition Test. |
| Species | Green alga (*Pseudokirchneriella subcapitata*) |
| Exposure Period | 72 hours |
| Concentration Range | Nominal: 0.625, 1.25, 2.5, 5.0, and 10 mg/L<br>Actual: 0.20, 0.46, 1.1, 2.2, 4.5 mg/L (time-weighted mean measured test concentrations) |
| Auxiliary Solvent | Not applied |
| Water Hardness | Not provided |
| Analytical Monitoring | The test concentrations were analysed at 0, 24, 48, and 72 hour of the test using HPLC. |
| Remarks - Method | Following a preliminary range-finding test, the definitive test was conducted at 24 ± 1°C with an initial cell concentration of 104.<br>The algal cell concentrations were determined using Coulter® Multisizer Particle Counter. Statistical analysis of the data was performed using the SAS computer software package (SAS, 1999 – 2001).<br>The test was conducted according to test guideline (TG) using good laboratory practice (GLP). |

RESULTS

| *Biomass* | | *Growth* | |
|---|---|---|---|
| *$E_bC50$ mg/L at 72 h* | *NOEC mg/L* | *$E_rC50$ mg/L at 72 h* | *NOEC mg/L* |
| 0.89 (95% CL 0.78 – 1.0) | 0.46 | 1.5 (95% CL 1.4 – 1.6) | 0.46 |

| | |
|---|---|
| Remarks - Results | All the test validity criteria were met.<br>The test concentrations declined significantly during the test: a decline between 43% to 58% at 24 hours, 14% to 27% at 48 hours, and between below the limit of quantification (LOQ) to 23% at 72 hours, of the nominal concentrations, were detected. Therefore, the tested endpoints were based on the time-weighted mean measured test concentrations.<br>The notified chemical is considered to be toxic to algae based on the $E_rC50$ value. |
| CONCLUSION | The notified chemical is toxic to algae. |
| TEST FACILITY | Harlan (2012) |

**C.2.4. Inhibition of microbial activity**

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical |
| METHOD | OECD TG 209 Activated Sludge, Respiration Inhibition Test.<br>EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test |
| Inoculum | Activated sludge |

| | |
|---|---|
| Exposure Period | 3 hours |
| Concentration Range | Nominal: 10, 32, 100, 320 and 1000 mg/L<br>Actual: not determined |
| Remarks – Method | The test was conducted at 21 ± 1°C. Chemical 3,5-dichlorophenol was used for the reference control. The respiration rate was determined by measurement of BOD during the test after 3 hours of exposure.<br>The test was conducted according to test guideline (TG) using good laboratory practice (GLP). |

RESULTS

| | |
|---|---|
| IC50 | 140 mg/L (95% CL 120 - 161 mg/L) |
| NOEC | 71 mg/L |
| Remarks – Results | All the test validity criteria were met. The notified chemical is considered not to be inhibitory to sludge microbial activity. |

| | |
|---|---|
| CONCLUSION | The notified chemical is not inhibitory to microbial activity. |
| TEST FACILITY | Harlan (undated) |

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