File No: LTD/1839

June 2015

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

# PUBLIC REPORT

## Mimosal

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/1839 | Firmenich Pty Limited | Mimosal | 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 of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

| *Hazard classification* | *Hazard statement* |
|---|---|
| Skin 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:

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

The environmental hazard classification according to the *Globally Harmonised System of 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 |

**Human health risk assessment**
Provided that the recommended controls are being adhered to, under the conditions of the occupational setting, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

Based on the information available, when used at ≤ 0.3% in deodorants, ≤ 0.4% in other cosmetic products, ≤ 2% in air fresheners and ≤ 0.9% in other household products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

**Recommendations**

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin Irritation (Category 2): H315 – Causes skin irritation
  - Skin Sensitisation (Category 1): H317 – May cause an allergic skin reaction

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

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation processes:
  - Avoid contact with skin 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 during reformulation processes:
  - Impervious gloves, eye protection, coveralls

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

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

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 0.3% in deodorants, ≤ 0.4% in other cosmetic products, ≤ 2% in air fresheners and ≤ 0.9% in other household products.

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.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

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

**Regulatory Obligations**

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 0.31% in deodorants, 0.4% in other cosmetic products, 2% in air fresheners and 0.9% in other 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 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 Pty Limited (ABN: 86 002 964 794)
73 Kenneth Rd
BALGOWLAH, NSW 2093

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

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

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
None.

## 2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Mimosal

MOLECULAR WEIGHT
< 500 Da

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

## 3. COMPOSITION

DEGREE OF PURITY
> 95%

## 4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: pale yellow liquid.

| Property | Value | Data Source/Justification |
|---|---|---|
| Melting Point/Freezing Point | 9 ± 0.5 °C | Measured |
| Boiling Point | 266 ± 2 °C at 98.0 kPa | Measured |
| Density | 989 kg/m$^3$ at 20 ± 0.5 °C | Measured |
| Vapour Pressure | 1.4 x 10$^{-4}$ kPa at 25 °C | Measured |
| Water Solubility | 0.051 g/L at 20 °C | Measured |
| Hydrolysis as a Function of pH | At 40 °C<br>pH 2 $t_{1/2}$ = 20 days<br>pH 8.5 $t_{1/2}$ = 9.6 days<br>pH 12 $t_{1/2}$ = 0.2 days | Measured |
| Partition Coefficient (n-octanol/water) | log Pow = 3.12 at 30 °C | Measured |
| Adsorption/Desorption | log $K_{oc}$ = 2.86 at 30 °C | Measured |

| | | |
|---|---|---|
| Dissociation Constant | Not Determined | The notified chemical does not contain any functional groups that are expected to dissociate in water. |
| Flash Point | 147 ± 2 °C at 101.3 kPa | Measured |
| Autoignition Temperature | 356 ± 5 °C | Measured |
| Explosive Properties | Not determined. | Contains no functional groups that would imply explosive properties. |
| Oxidising Properties | Not determined. | Contains no functional groups that would imply oxidising properties. |

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

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

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

## 5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia at 100% concentration, as well as a component of compounded fragrance formulations and various formulated end-use cosmetic and household products (at concentrations ≤ 2%).

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.

IDENTITY OF MANUFACTURER/RECIPIENTS
Firmenich Pty Limited.

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 100% concentration) will be imported into Australia in lacquered drums of sizes ranging from 5 kg up to 180 kg. The end-use products (≤ 2% 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. The content in the final consumer products will vary, with the following proposed usage concentrations: cosmetic products (≤ 0.4%), air fresheners (≤ 2%) and other household products (≤ 0.9%).

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

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

household products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes.

*Household products*
Household products containing the notified chemical (≤ 2% 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.

*Cosmetics*
The finished cosmetic products containing the notified chemical at ≤ 0.4% 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 | unspecified | unspecified |
| Mixer | 4 | 2 |
| Drum Handling | 4 | 2 |
| Drum Cleaning | 4 | 2 |
| Maintenance | 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 notified chemical, at 100% concentration or as a component of the imported fragrance preparations (≤ 2% concentration) or end-use products (≤ 2% 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, 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 (at ≤ 2% concentration) in end-use products may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal,

while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

### 6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of the cosmetic and household products (≤ 2% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

A combined internal dose of 0.9964 mg/kg bw/day was estimated using data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used (SCCS, 2012; Cadby *et al.*, 2002; Loretz *et. al.*, 2006; ACI, 2010; specific use details of the notified chemical are considered as exempt information). 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 > 2,000 mg/kg bw; low toxicity |
| Rat, acute dermal toxicity | LD50 > 2,000 mg/kg bw; low toxicity |
| Rat, acute inhalation toxicity | LC50 > 5.31 mg/L/4 hours; 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 (3%) | no evidence of sensitisation |
| Rat, repeat dose oral toxicity – 28 days. | NO(A)EL 300 mg/kg bw/day |
| Mutagenicity – bacterial reverse mutation | non mutagenic |
| Genotoxicity – in vitro mammalian chromosome aberration test. | non genotoxic |

*Toxicokinetics, metabolism and distribution.*
Based on the water solubility (0.051 g/L at 20 ºC), partition coefficient (log $P_{ow}$ = 3.12) and the low molecular weight (< 500 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are possible. The notified chemical may also be absorbed across the respiratory tract.

*Acute toxicity.*
The notified chemical was found to have low acute toxicity in rats via the oral, dermal and inhalation routes. It is noted, however, that signs of toxicity were reported in the acute inhalation study (e.g. increased respiratory rate – noted up to day 9 post-exposure).

*Irritation.*
In an acute dermal irritation study in rabbits, a single 4-hour, semi-occluded application of the notified chemical resulted in well-defined erythema (with loss of skin elasticity) and very slight-slight oedema at all sites at the 24 hour observation, which was still evident at the 72 hour observation. At the 7 day observation, all treated sites showed moderate desquamation, with 2 animals exhibiting small superficial scattered scabs and hardened light brown coloured scabs. Additional glossy skin was noted underneath the scab at 1 site, with the effects at this site preventing evaluation of the degree of erythema. At the end of the observation period, 2 sites exhibited glossy skin. The effects in this study warrant classification of the notified chemical as a dermal irritant.

In an acute ocular irritation study in rabbits, a single instillation of the notified chemical resulted in slight-moderate conjunctival irritation (3/3 animals) and iridial inflammation (1/3 animals) at the 24 hour observation, with all animals appearing normal by the 72 hour observations. The effects in this study did not warrant classification of the chemical as an eye irritant.

*Sensitisation.*

The notified chemical was a skin sensitiser in mice (Local Lymph Node Assay; tested at 5, 25, 50 and 100% concentration, with stimulation indices of 2.12, 6.19, 13.93 and 15.06, respectively). The $EC_3$ value was calculated to be 9%.

In a human repeat insult patch test (HRIPT; 105 subjects completing the study), the notified chemical (at 3% concentration) was not considered by the study authors to induce skin sensitisation.

*Repeated dose toxicity*
In a 28 day repeat dose study by oral gavage, rats were administered the notified chemical at 30, 300 and 750 mg/kg bw/day. A diverse range of clinical observations, haematological and biochemical findings were observed in test animals of both sexes across the dosed groups (many with statistical significance), for example, reduced body weight gains seen in high dose males and females, increased water consumption, decreased mean plasma bilirubin levels, decreased mean corpuscular haemoglobin and mean lymphocyte counts and increased mean sodium and phosphorus levels. While these variations were largely deemed not to be of toxicological significance by the study authors, the study authors could not discount a relationship to treatment for the observed electrolyte level disruptions, given that there was histopathological evidence of impaired renal function (see below).

Changes in organ weights of note included the elevated mean absolute and relative kidney and liver weights (statistically significant), seen in the high dose males. Microscopic findings seen in the kidneys of animals of both sexes in the mid and high dose groups included basophilic epithelium in the collecting tubules, with some animals showing the more severe effects of associated single cell necrosis and/or increased mitoses.

While renal findings were noted at both the mid and high dose levels, given the frequency and severity of effects at the mid dose level, the study authors established the No Observed (Adverse) Effect Level (NO(A)EL) as 300 mg/kg bw/day in this study, with the NOEL established as 30 mg/kg bw/day.

*Mutagenicity/Genotoxicity.*
The notified chemical was not mutagenic in a bacterial reverse mutation study and non-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 of 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 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 ≤ 100% concentration) may occur during blending operations. The notified chemical has the potential to cause skin irritation and is considered to be a skin sensitiser. In addition, harmful effects following inhalation and/or repeated exposure to the notified chemical are possible. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

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

*End-use*
Cleaners and beauty care professionals will handle the notified chemical at ≤ 2% concentration, similar to public use. Therefore, the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

### 6.3.2. Public Health

*Irritation*
The notified chemical has the potential to cause irritation to skin and slight irritation to the eyes. However, skin and eye irritation effects are not expected from use of the notified chemical at the proposed concentrations in cosmetic and household products.

*Skin sensitisation*
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). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in a number of different cosmetic products may be estimated (SCCS, 2012 and Cadby *et al*, 2002).

Following consideration of the available data on skin sensitisation (and the study details/results of these studies) and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 22.25 μg/cm$^2$ was derived (using the EC3 value of 9%, which was obtained in an LLNA study on the notified chemical). In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of ~100.

| **Product type** | **Proposed maximum usage concentration (%)** | **CEL chemical** (μg/cm$^2$) | **AEL chemical** (μg/cm$^2$) | **Proposed usage concentration supported?** | **Recommended usage concentration (%)** |
|---|---|---|---|---|---|
| Deodorant | 0.4 | 30.00 | 22.25 | No | ≤ 0.3 |
| Other cosmetics (assumed: fine fragrances) | 0.4 | 15.00 | 22.25 | Yes | ≤ 0.4* |

*Proposed usage concentration

As the CEL > AEL for deodorant, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical in this product type at ≤ 0.4% concentration is considered to be unreasonable. Reducing the concentration of the notified chemical in deodorant to 0.3% allows recalculation of the consumer exposure to an acceptable level. As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical in other cosmetics (using fine fragrances as a worst case example) at ≤ 0.4% concentration is not considered to be unreasonable.

Based on the lower expected exposure level from use of household products (≤ 2% notified chemical), by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

*Repeated dose toxicity*
Members of the public may experience repeated exposure to the notified chemical through the use of the cosmetic and household products (≤ 2% concentration in individual products).

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.9964 mg/kg bw/day (see Section 6.1.2) and the NO(A)EL of 300 mg/kg bw/day, which was established by the study authors 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 (noting the effects that were observed at the NOAEL, which was derived from a 28-day study). Using the abovementioned NO(A)EL, a MoE of 301 was estimated, which is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.3% in deodorants, ≤ 0.4% in other cosmetic products, ≤ 2% in air fresheners and ≤ 0.9% in other 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 not be manufactured in Australia, so there will be no environmental release associated with this activity. The notified chemical will be imported into Australia at 100% concentration, in the form of fragrance preparations for further reformulation into end-use cosmetic and household products or as a component of end-use products. Environmental release of the notified chemical during transportation and storage will be limited to accidental spills or leaks of drums, which is expected to be minimal.

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

RELEASE OF CHEMICAL FROM USE

The notified chemical will enter the aquatic compartment during use of the various products into which it will be incorporated. Cosmetic products are expected to be washed off the hair and skin and will enter the aquatic environment diluted in water. Cleaning products will also be diluted in water and will enter the aquatic environment. It is anticipated that the majority of the notified chemical released will enter into sewer systems.

It is estimated that a maximum of 3% of the consumer products may remain in the consumer containers that will be sent for disposal.

RELEASE OF CHEMICAL FROM DISPOSAL

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

#### 7.1.2. Environmental Fate

The notified chemical is not readily biodegradable based on the provided test report (29 – 48% in 28 days). For the details of the environmental fate studies please refer to Appendix C. The notified chemical is expected to undergo significant hydrolysis. Based on its low adsorption coefficient value (log $K_{oc}$ = 2.86), only limited partitioning to sludge is expected. The notified chemical has low potential to bioaccumulate based on its low partition coefficient (log $P_{ow}$ = 3.12). 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 half-life of the notified chemical in air is calculated to be 1.095 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.

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 predicted environmental concentration (PEC) has been calculated assuming a worst case scenario of 100% release of the notified chemical into sewer systems nationwide and no removal from STPs.

***Predicted Environmental Concentration (PEC) for the Aquatic Compartment***

| | | |
|---|---|---|
| Total Annual Import/Manufactured Volume | 1,000 | kg/year |
| Proportion expected to be released to sewer | 100% | |
| Annual quantity of chemical released to sewer | 1,000 | kg/year |
| Days per year where release occurs | 365 | days/year |
| Daily chemical release: | 2.74 | kg/day |
| Water use | 200 | L/person/day |
| Population of Australia (Millions) | 22.613 | million |
| Removal within STP | 0% | |
| Daily effluent production: | 4,523 | ML |
| Dilution Factor - River | 1.0 | |
| Dilution Factor - Ocean | 10.0 | |
| PEC - River: | 0.61 | µg/L |
| PEC - Ocean: | 0.06 | µg/L |

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/$m^2$/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/$m^3$). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

### 7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. The provided studies include acute toxicity of the notified chemical to aquatic invertebrates and algae, and inhibition of activated sludge. Details of these studies can be found in Appendix C.

| Endpoint | Result | Assessment Conclusion |
|---|---|---|
| Daphnia Toxicity (48 hours) | $EC_{50}$ = 1.1 mg/L | Toxic to aquatic invertebrates |
| Algal Toxicity (72 hours) | $ErC_{50}$ = 2.6 mg/L | Toxic to algae |
| Inhibition of Bacterial Respiration (3 hours) | $EC_{50}$ > 100 mg/L | Not Inhibitory to microbial respiration |

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is toxic to fish, aquatic invertebrates and algae, and is formally classified as 'Acute Category 2: Toxic to aquatic life'. Based on the acute toxicity, lack of ready biodegradability and low bioaccumulation potential of the notified chemical, it is not expected to be harmful to aquatic life on a long term basis, and is therefore not formally classified under the GHS.

#### 7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the most sensitive toxicity endpoint of the notified chemical among the two test species. The most conservative assessment factor of 1,000 was used since only two trophic levels of ecotoxicological data (invertebrates and algae) have been provided for the PNEC analysis.

| ***Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment*** | | |
|---|---|---|
| EC50 (Invertebrates). | 1.10 | mg/L |
| Assessment Factor | 1,000 | |
| PNEC: | 1.10 | µg/L |

### 7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated for a worst case discharge scenario based on the predicted PEC and PNEC.

| ***Risk Assessment*** | ***PEC µg/L*** | ***PNEC µg/L*** | ***Q*** |
|---|---|---|---|
| Q - River: | 0.61 | 1.1 | 0.555 |
| Q - Ocean: | 0.06 | 1.1 | 0.055 |

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment ($Q < 1$) indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The notified chemical is not expected to be readily biodegradable or bioaccumulate in the environment. Therefore, the notified chemical is unlikely to result in ecotoxicologically significant concentrations in the aquatic environment on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern.

## APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

**Melting Point/Freezing Point** 9 ± 0.5 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Carried out in duplicate using a dry ice/isopropanol bath.
Test Facility Firmenich (2012a)

**Boiling Point** 266 ± 2 °C at 98.0 kPa

Method OECD TG 103 Boiling Point.
Remarks Determined according to the Siwoloboff method.
Test Facility Firmenich (2012a)

**Density** 989 kg/m$^3$ at 20 ± 0.5 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Determined using the oscillating density meter method
Test Facility Firmenich (2012a)

**Vapour Pressure** 1.4 x $10^{-4}$ kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
Remarks Determined using the gas saturation method.
Test Facility Harlan (2014a)

**Water Solubility** 0.051 g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method. The concentration of test material in the sample solutions was determined by high performance liquid chromatography (HPLC).
Test Facility Firmenich (2012a)

**Hydrolysis as a Function of pH** At 40 °C: pH 2 $t_{1/2}$ = 20 days; pH 8.5 $t_{1/2}$ = 9.6 days; pH 12 $t_{1/2}$ = 0.2 days

Method 200 – 300 ppm of the notified chemical was dissolved in a pH buffer containing the surfactant (Arkopal N 150) and put into storage in an oven at 40 °C. Small aliquots of the test solution were extracted with an organic solvent (typically cyclohexane or ethyl acetate) containing a hydrocarbon standard (typically C12, C17 or C20) on a regular basis throughout the test (typically at time = 0, 0.25, 1, 2, 4, 7, 15, 21 and 28 days). The extracts were analyzed by GC-FID and the results plotted as (Area/Area Std) expressed in [%]. The measurement at time = 0 was set at 100% and the succeeding measurements were calculated relatively to the time = 0 measurement. Therefore, the curves represent the percentage of product remaining in the test solution at the time of analysis.

| *pH* | *T (°C)* | *t½ days* |
|---|---|---|
| 2 | 40 | 20 |
| 8.5 | 40 | 9.6 |
| 129 | 40 | 0.2 |

Remarks At pH 5 and 40 °C, the notified chemical was hydrolytically stable, less than 5% disappeared after 28 days. At pH 7 and 40 °C, 12% the notified chemical disappeared after 5 days and 31% after 28 days.
Test Facility Firmenich (2012a)

**Partition Coefficient (n-octanol/water)** log $P_{ow}$ = 3.12 at 30 °C

| | |
|---|---|
| Method | OECD TG 117 Partition Coefficient (n-octanol/water). |
| Remarks | HPLC Method. The notified chemical and reference standard solutions were injected in quintuplicate. |
| Test Facility | Firmenich (2012a) |

**Adsorption/Desorption – screening test** log $K_{oc}$ = 2.86 at 30 °C

| | |
|---|---|
| Method | OECD TG 121: Estimation of the Adsorption Coefficient ($K_{oc}$) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC) and Method C19 Adsorption Coefficient of Commission Regulation (EC) No 440/2008 |
| Remarks | The test item contains no functional groups which would dissociate in the normal environmental pH range (approximately pH 5.5 to pH 7.5); therefore testing was performed without adjusting the pH of the mobile phase. As the slope of the calibration curve for the reference standards showed good first order correlation and as the retention times between duplicate injections for each solution were consistent, the HPLC method was considered valid for the determination of the adsorption coefficient. Based on the chromatographic data, the test item was considered to be stable during the test procedure. |
| Test Facility | Harlan (2014b) |

**Flash Point** 147 ± 2 °C at 101.3 kPa

| | |
|---|---|
| Method | EC Council Regulation No 440/2008 A.9 Flash Point. |
| Remarks | Determined using a closed cup equilibrium method. |
| Test Facility | Firmenich (2012a) |

**Autoignition Temperature** 356 ± 5 °C

| | |
|---|---|
| Method | EC Directive 440/2008/EC A.15 Auto-Ignition Temperature (Liquids and Gases). |
| Remarks | Determined by heating aliquots of the test material in a flask and observing any ignition.<br>Conducted at atmospheric pressure ranging from 100.7 to 101.4 kPa.<br>At test temperatures ≥ 356 °C, orange/blue flame with emission of grey fumes was observed. |
| Test Facility | Harlan (2012a) |

# APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

## B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 420 Acute Oral Toxicity – Fixed Dose Method.
- Species/Strain: Rat/RccHan™:WIST
- Vehicle: Arachis oil BP (300 mg/kg bw) or none (2,000 mg/kg bw)
- Remarks - Method: No significant protocol deviations. GLP Compliance.

RESULTS

Sighting Study

| *Group* | *Number and Sex of Animals* | *Dose mg/kg bw* | *Mortality* |
|---|---|---|---|
| 1 | 1 F | 300 | 0/1 |
| 2 | 1 F | 2,000 | 0/1 |

- Signs of Toxicity: None.
- Effects in Organs: None.

Main Study

| *Group* | *Number and Sex of Animals* | *Dose mg/kg bw* | *Mortality* |
|---|---|---|---|
| 1 | 4 F | 2,000 | 0/4 |

- $LD_{50}$: > 2,000 mg/kg bw
- Signs of Toxicity: There were no treatment related signs of systemic toxicity noted in any of the animals over the study period.
- Effects in Organs: Dark liver was noted in 1 animal at necropsy.
- Remarks - Results: All animals gained weight over the course of the study.

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

TEST FACILITY: Harlan (2012b)

## B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 402 Acute Dermal Toxicity– Limit Test.
- Species/Strain: Rat/RccHan™:WIST
- Vehicle: None.
- Type of dressing: Semi-occlusive.
- Remarks - Method: No significant protocol deviations. GLP Compliance.

RESULTS

| *Group* | *Number and Sex of Animals* | *Dose mg/kg bw* | *Mortality* |
|---|---|---|---|
| 1 | 5 per sex | 2,000 | 0/10 |

- $LD_{50}$: > 2,000 mg/kg bw
- Signs of Toxicity - Local: No clinical signs of dermal irritation were noted in any of the animals over the study period.
- Signs of Toxicity - Systemic: There were no treatment related signs of systemic toxicity noted in any of

| | |
|---|---|
| | the animals over the study period. |
| Effects in Organs | No macroscopic findings were seen in any of the animals at necropsy. |
| Remarks - Results | 3 female animals showed body weight loss or no gain during the 1st week of the study, however gains were shown in the second week. All other animals gained weight over the course of the study. |

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

TEST FACILITY Harlan (2014c)

### B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical.

| METHOD | OECD TG 436 Acute Inhalation Toxicity – Acute Toxic Class Method |
|---|---|
| Species/Strain | Rat/RccHan$^{TM}$:WIST |
| Vehicle | None. |
| Method of Exposure | Nasal exposure only. |
| Exposure Period | 4 hours |
| Physical Form | Liquid aerosol. |
| Particle Size | MMAD 1.93 ± 2.65 μm (77.4% < 4 μm) |
| Remarks - Method | No significant protocol deviations.<br>GLP Compliance. |

RESULTS

| *Group* | *Number and Sex of Animals* | *Concentration mg/L* | | *Mortality* |
|---|---|---|---|---|
| | | *Nominal* | *Actual* | |
| 1 | 3 per sex | 18.8 | 5.31 ± 0.22 | 0/6 |

| | |
|---|---|
| $LC_{50}$ | > 5.31 mg/L/4 hours |
| Signs of Toxicity | A variety of clinical observations were seen in all test animals, for varying duration of effect. These included wet fur (noted 1 hour into exposure to 1 hour post-exposure), hunched posture (at removal from the chamber up to day 3 post exposure), pilo-erection (at removal from the chamber up to day 1 post exposure), increased respiratory rate (2 hours into exposure up to day 9 post exposure), red/brown staining around the eyes and/or snout (only noted in 2 females at removal from the chamber and 1 hour post-exposure). |
| Effects in Organs | No macroscopic findings were seen in any of the animals at necropsy. |
| Remarks - Results | 2 females and 2 males showed body weight losses on day 1 post exposure, with this loss continuing in 1 of the females and noted in another female. From day 3 to the end of the study period, all test animals showed weight gains at the weekly observations. |

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY Harlan (2013a)

### B.4. Irritation – skin

TEST SUBSTANCE Notified chemical.

| METHOD | OECD TG 404 Acute Dermal Irritation/Corrosion. |
|---|---|
| Species/Strain | Rabbit/New Zealand White |
| Number of Animals | 3 M |
| Vehicle | None. |
| Observation Period | 14 days |
| Type of Dressing | Semi-occlusive. |

Remarks - Method
No significant protocol deviations.
GLP Compliance.

RESULTS

| *Lesion* | *Mean Score* Animal No.* | | | *Maximum Value* | *Maximum Duration of Any Effect* | *Maximum Value at End of Observation Period* |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | | |
| *Erythema/Eschar* | 2 | 2 | 2 | 2 | < 14 days | 0 |
| *Oedema* | 2 | 1.66 | 2 | 2 | < 14 days | 0 |

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

Remarks - Results
Very slight erythema and very slight to slight oedema was noted at all treated sites immediately after patch removal and at 2 sites at the 1 hour observation. Effects increased in severity (well defined erythema at all sites, with loss of skin elasticity and slight oedema) by the 24 hour observation and were still evident at the 72 hour observation.

At the 7 day observation, all treated sites showed moderate desquamation. 2 animals exhibited small superficial scattered scabs and hardened light brown coloured scabs. Additional glossy skin was noted underneath the scab at 1 site, with the effects at this site preventing evaluation of the degree of erythema. Oedema had resolved in 2 of the animals.

At the end of the observation period, 2 sites exhibited glossy skin.

CONCLUSION
The notified chemical is irritating to the skin.

TEST FACILITY
Harlan (2012c)

**B.5. Irritation – eye**

TEST SUBSTANCE
Notified chemical.

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

A Rabbit Enucleated Eye Test (REET) was performed (using enucleated eyes taken from NZW male rabbits; 3 treated and 2 controls) prior to this study to assess the ocular irritancy potential of the test item. Based on the results, the test item was considered unlikely to have the potential to cause severe ocular irritancy *in vivo*.

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 | 1 | 0.66 | 2 | < 72 hours | 0 |
| *Conjunctiva: chemosis* | 0.33 | 0.66 | 0.33 | 2 | < 72 hours | 0 |
| *Conjunctiva: discharge* | 0 | 0.33 | 0 | 1 | < 48 hours | 0 |
| *Corneal opacity* | 0 | 0 | 0 | 0 | - | 0 |
| *Iridial inflammation* | 0.33 | 0 | 0 | 1 | < 48 hours | 0 |

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

| | |
|---|---|
| Remarks - Results | No corneal effects were noted. Iridial inflammation was noted in one treated eye 1 hour after treatment and at the 24 hour observation.<br><br>Slight to moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment. All treated eyes had recovered by the 72 hour observations. |
| CONCLUSION | The notified chemical is slightly irritating to the eye. |
| TEST FACILITY | Harlan (2012d) |

**B.6. Skin sensitisation – mouse local lymph node assay (LLNA)**

| | |
|---|---|
| TEST SUBSTANCE | Notified chemical. |
| METHOD | OECD TG 429 Skin Sensitisation: Local Lymph Node Assay |
| Species/Strain | Mouse/ CBA/CaOlaHsd |
| Vehicle | Acetone/olive oil (AOO; 4:1) |
| Remarks - Method | GLP Compliance.<br><br>A preliminary toxicity study was performed with the undiluted test substance (1 mouse) and was used to select the concentrations for the main test. Mean ear thickness measurements changed by < 20% over 6 days in this test.<br><br>Based on the results of the main study (conducted at 25%, 50% and 100% concentration), additional animals were tested with the test substance at 5% v/v concentration (dilution in AOO) and the vehicle control. These groups were treated in a similar manner as groups in the initial test.<br><br>A concurrent positive control study was not run, but had been previously run using α-Hexylcinnamaldehyde. |

RESULTS

| *Concentration (% v/v)* | *Proliferative response (DPM/animal)* | | *Stimulation Index (Test/Control Ratio)* |
|---|---|---|---|
| *Test Substance* | | | |
| 0 (vehicle control) | 2,371.39 (± 595.04) | 2,279.81 (± 2360.18) | - |
| 5 | - | 4,838.93 (± 1554.49) | 2.12 |
| 25 | 14,685.11 (± 3,745.96) | - | 6.19 |
| 50 | 33,023.91 (± 4,411.90) | - | 13.93 |
| 100 | 35,721.32 (± 4,145.47) | - | 15.06 |

| | |
|---|---|
| Remarks - Results | No signs of systemic toxicity or excessive local irritation were noted during the course of the study.<br><br>An EC3 of 9% was calculated for the notified chemical. It is noted that a large proliferative response was seen for one of the animals in the vehicle control group (additional test; 6,464.46 DPM/animal), which if discounted as an outlier, would have resulted in a lower mean response and subsequently, a higher stimulation index (> 3) being recorded at the 5% concentration. However, it is also noted that the mean vehicle control value used (2,279.81 DPM/animal) is similar to the vehicle control value recorded in the initial phase of the main test (2,371.39). |
| CONCLUSION | There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical. |

TEST FACILITY Harlan (2013b)

### B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (3%)

METHOD Repeated insult patch test with challenge.

Study Design
Induction Procedure: Patches containing 0.3 mL test substance were applied 3 times per week for a total of 9 applications. Patches were removed by the subjects after 24 hours and graded after an additional 24 hours (or 48 hours for patches applied prior to weekends).

Rest Period: approximately 2 weeks

Challenge Procedure: A patch was applied to a naïve site. Patches were removed by technicians after 24 hours and the sites graded. Sites were additionally graded 24, 48 and 72 hours post-patch removal.

Study Group 85 F, 35 M; age range 18 – 79 years

Vehicle 75% diethyl phthalate / 25% ethanol mixture.

Remarks - Method Occluded. The test substance was spread on a 2.54 $cm^2$ patch, and allowed to evaporate for 15 – 40 minutes prior to patch application.

RESULTS

Remarks - Results 105/120 subjects completed the study. The 15 subjects who discontinued were deemed by study authors to do so for reasons unrelated to the test material (0 – 9 induction observations recorded).

A female subject presented with effects during the induction phase. Faint, minimal erythema was noted at induction readings 4, 8 and 9, with more pronounced erythema noted at readings 5, 6 and 7. No reactions were noted for this subject during the challenge phase.

No reactions were evident in any other test subject during the induction and challenge phases.

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

TEST FACILITY HRL (2015)

### 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 Han™:RccHan™:WIST

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.
GLP Compliance.

RESULTS

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

*Mortality and Time to Death*

There were no unscheduled deaths or moribund/debilitated animals that needed to be sacrificed before necropsy.

*Clinical Observations*

Treatment-related clinical findings included sporadic transient episodes of increased salivation. This was seen in all animals of both sexes from day 4 in the high dose group and from day 8 in the mid dose group and persisted through to the final week of treatment. The study authors considered these observations to be indicative of the unpleasant tasting or slightly irritant nature of the test item and not representative of systemic toxicity.

No functional observations were deemed by the study authors to be of toxicological significance. Decreased (statistically significant) results in one of the hindlimb grip strength tests were seen in all male treatment groups (considered by the study authors to be incidental in the absence of a dose-response relationship or other supporting evidence of neurotoxicity). No effect was seen in the corresponding females.

The body weight gain of the high dose group males over the course of the treatment period was slightly reduced compared to the equivalent control animals. This was also noted in the high dose group females during week 3 and 4 of the treatment period. However, this was not deemed by the study authors to be of toxicological significance. No other significant body weight changes were noted for the other dose groups relative to control animals.

Some effects on food and water consumption were noted during the study period. Females of all 3 treatment groups showed reduced food consumption compared to controls over the course of the study period, however this did not correspond to significant effects on food efficiency and was not seen in the male groups. Water consumption was slightly increased compared to controls in male animals from the mid and high dose groups (analysis conducted in week 3 of the study). The study authors proposed a causal link between the palatability issues of the test item and the subsequent compensatory increase in water consumption.

*Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis*

The following statistically significant ($p < 0.05$) effects were seen in the clinical chemistry of the study animals:

| Treatment | Females | Males |
|---|---|---|
| 750 | ↑ mean plasma phosphorus concentration | ↑ mean sodium levels<br>↓ mean plasma bilirubin levels<br>↑ mean albumin/globulin ratio |
| 300 | - | ↓ mean plasma bilirubin levels* |
| 30 | - | ↓ mean plasma bilirubin* and chloride levels |

* ($p < 0.01$)

The study authors did not deem the differences in the albumin/globulin ratio, plasma bilirubin levels and plasma chloride levels to be of toxicological significance, as they did not show a dose-dependent trend, fell within the historical ranges and/or lacked histopathological evidence of associated liver changes. However, the study authors considered that as there was histopathological evidence of impaired renal function, a relationship to treatment for the observed electrolyte level disruptions (changes seen in sodium and phosphorus levels) could not be discounted.

Statistically significant ($p < 0.05$) differences noted in specific haematological parameters compared to control animals included:

| Treatment | Females | Males |
|---|---|---|
| 750 | ↓ mean corpuscular haemoglobin (MCH)<br>↓ mean corpuscular haemoglobin concentration* | ↓ mean corpuscular haemoglobin (MCH)<br>↓ mean corpuscular haemoglobin concentration |
| 300 | - | ↓ mean corpuscular haemoglobin (MCH)<br>↓ mean lymphocyte count |
| 30 | - | ↓ mean lymphocyte count |

* ($p < 0.01$)

The study authors did not deem these differences to be of toxicological significance, as the variant values in MCH almost all fell within the historical ranges and the lymphocyte count changes did not show a dose-

dependent trend. The study authors also suggested an association between an oral irritation/palatability-induced dehydration and minor haematological blood concentration changes.

*Effects in Organs*
No macroscopic abnormalities were noted at necropsy.

The following statistically significant ($p < 0.05$) effects were seen on organ weights:

| Treatment | Females | Males |
|---|---|---|
| 750 | ↑ ovary weights (both absolute & relative) | ↑ kidney weight (both absolute & relative)<br>↑ liver weight (both absolute & relative)*<br>↓ pituitary weight (both absolute & relative)* |
| 300 | - | ↓ pituitary weight (both absolute & relative) |
| 30 | ↑ spleen weight (both absolute & relative)* | - |

* ($p < 0.01$)

The study authors did not deem the spleen, pituitary and ovary effects to be of toxicological significance, as the variant weight values almost all fell within the historical ranges and lacked supporting histopathological correlates. However, given the overall observed effects, a relationship to treatment for the increased liver and kidney weights could not be discounted.

Toxicologically significant microscopic abnormalities were noted at histopathological examination. Kidney effects including minimal or mild basophilia of the epithelium in the collecting tubules were seen in animals of both sexes of the mid (4/5M & 1/5F) and high (5/5M & 4/5F) dose groups. In the more severely affected animals there was associated single cell necrosis and/or increased mitoses. No treatment related effects on organs were detected in animals of the low dose group.

Remarks – Results
While renal findings were noted at both the mid and high dose levels, given the frequency and severity of the findings at the mid dose level, the study authors considered this level to be the NOAEL.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established by the study authors as 300 mg/kg bw/day in this study. The No Observed Effect Level (NOEL) was established by the study authors as 30 mg/kg bw/day.

TEST FACILITY Harlan (2014d)

**B.9. Genotoxicity – bacteria**

TEST SUBSTANCE Notified chemical

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

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

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

Concentration Range in Main Tests
a) With metabolic activation: 0.5 – 500 µg/plate
b) Without metabolic activation: 0.15 – 150 or 500 (WP2uvrA) µg/plate

Vehicle Dimethyl sulphoxide (DMSO)

Remarks - Method
No significant protocol deviations.
GLP Compliance.
Tests 1 and 2 were performed using the direct plate incorporation and pre incubation methods, respectively.

A preliminary toxicity test (0.15 – 5,000 µg/plate; plate incorporation) was performed for strains TA100 and WP2uvrA (with and without S9-mix) to determine the toxicity of the test material. Precipítate (light and oily) was noted in plates at ≥ 5,000 µg/plate.

Test 1 was conducted using the plate incorporation procedure, while Test

2 was conducted using the pre-incubation procedure.

Positive control tests were conducted in parallel to the main test using 9-aminoacridine, 4-nitroquinoline-1-oxide and N-ethyl-N'-nitro-N-nitrosoguanidine in the absence of S9-mix; 2-anthramine and benzo(a)pyrene with S9-mix.

RESULTS

| *Metabolic Activation* | *Test Substance Concentration (µg/plate) Resulting in:* | | | |
|---|---|---|---|---|
| | *Cytotoxicity in Preliminary Test* | *Cytotoxicity in Main Test* | *Precipitation* | *Genotoxic Effect* |
| *Absent* | | | | |
| Test 1 | ≥ 150 | ≥ 150 | > 150 (or > 500) | negative |
| Test 2 | | ≥ 15 | > 150 (or > 500) | negative |
| *Present* | | | | |
| Test 1 | ≥ 150 | ≥ 150 | > 500 | negative |
| Test 2 | | ≥ 150 | > 500 | negative |

Remarks - Results

Visible reduction in the growth of the bacterial background lawn was seen in all tester strains, with and without metabolic activation.

No increases in the frequency of revertant colonies were recorded for any of the bacterial strains.

The positive controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY

Harlan (2013c)

**B.10. Genotoxicity – in vitro**

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Human

Cell Type/Cell Line: Lymphocytes/peripheral

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

Vehicle: DMSO

Remarks - Method: No significant protocol deviations.
GLP Compliance.

A preliminary toxicity study was performed (4 hour exposure and 20 hour recovery period, with and without activation and 24 hour exposure without activation) at concentrations 7.34 – 1,880 µg/mL. Precipitates were noted at ≥ 940 µg/mL (greasy/oily; 4 hour exposure groups) and ≥ 235 µg/mL (greasy/oily and cloudy; 24 hour exposure). Haemolysis was noted at ≥ 58.75 µg/mL and ≥ 117.5 µg/mL (4 hour exposure) in the absence and presence of S9 mix, respectively, and at ≥ 117.5 µg/mL following the 24hour exposure period.

Vehicle and positive controls (mitomycin C without metabolic activation and cyclophosphamide with metabolic activation) were used in parallel with the test material.

| *Metabolic Activation* | *Test Substance Concentration (µg/mL)* | *Exposure Period* | *Harvest Time* |
|---|---|---|---|

| | | | |
|---|---|---|---|
| *Absent* | | | |
| Test 1 | 0*, 3.75, 7.5*, 15*, 30*, 60, 120 | 4 hours | 24 hours |
| Test 2 | 0*, 3.75, 7.5*, 15*, 30*, 40*, 60 | 24 hours | 24 hours |
| *Present* | | | |
| Test 1 | 0*, 15*, 30*, 60*, 80, 100, 120 | 4 hours | 24 hours |
| Test 2 | 0*, 7.5, 15*, 30*, 60*, 80, 100 | 4 hours | 24 hours |

*Cultures selected for metaphase analysis.

RESULTS

| *Metabolic Activation* | *Test Substance Concentration (μg/mL) Resulting in:* | | | |
|---|---|---|---|---|
| | *Cytotoxicity in Preliminary Test* | *Cytotoxicity in Main Test* | *Precipitation* | *Genotoxic Effect* |
| *Absent* | | | | |
| Test 1 | ≥ 58.75 | ≥ 30 | > 120 | Negative |
| Test 2 | ≥ 58.75 | ≥ 40 | > 60 | Negative |
| *Present* | | | | |
| Test 1 | ≥ 117.5 | ≥ 80 | > 120 | Negative |
| Test 2 | | ≥ 60 | > 100 | Negative |

Remarks - Results

No statistically significant increases in the frequency of cells with chromosomal aberrations or number of polyploidy cells were seen at any dose level, with and without metabolic activation.

In test 1, haemolysis was noted at ≥ 60 μg/mL and ≥ 80 μg/mL in the absence and presence of S9 mix, respectively. In test 2, haemolysis was noted at ≥ 60 μg/mL in the presence of S9 mix.

The study authors noted the steepness of the toxicity curve (e.g. Test 1 in the presence of metabolic activation: no marked reduction in mitotic index noted at 60 μg/mL and insufficient cells and metaphases for scoring at 80 μg/mL).

The positive controls produced satisfactory responses, thus confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Harlan (2014e)

# 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 | None Reported |
| Analytical Monitoring | Biochemical Oxygen Demand (BOD) |
| Remarks - Method | No significant protocol deviations.<br>GLP Compliance |

The test material, at a concentration of 99.95 mg/L in test 1, at a concentration of 100.1 mg/L in test 2 and at a concentration of 99.85 mg/L in test 3, was exposed to activated sewage sludge micro-organisms with culture medium in sealed culture vessels in diffused light at 22 ± 1 °C. The degradation of the test material was assessed by the measurement of daily oxygen consumption on days 0 and 28. Test 3 results shown below.

RESULTS

| *Test substance* | | *Sodium benzoate* | |
|---|---|---|---|
| *Day* | *% Degradation* | *Day* | *% Degradation* |
| 1 | -2 | 1 | 22 |
| 7 | -3 | 7 | 76 |
| 14 | 20 | 14 | 86 |
| 20 | 33 | 20 | 93 |
| 28 | 40 | 28 | 93 |

Remarks - Results: All the test validity criteria were met. The test material (test 1, 2 and 3) attained respectively 29, 48 and 40% degradation after 28 days. The results of the degradation test are considered valid because the reference material reached ≥ 60% degradation by Day 14.

CONCLUSION: The notified chemical is not readily biodegradable

TEST FACILITY: Firmenich (2014)

## 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 and Reproduction Test-Semi Static

| | |
|---|---|
| Species | *Daphnia magna* |
| Exposure Period | 48 hours |
| Auxiliary Solvent | None Reported |
| Water Hardness | 250 mg $CaCO_3$/L |
| Analytical Monitoring | High performance liquid chromatography with UV detection (HPLC/UV) |
| Remarks - Method | No significant protocol deviations.<br>GLP Compliance. |

The control group was maintained under identical conditions but not

exposed to the test item. The test concentrations to be used in the definitive test were determined by a preliminary range-finding test. In the range-finding test *Daphnia magna* were exposed to a series of nominal test concentrations of 0.10, 1.0, 10 and 100% v/v saturated solution. Based on the results of the range-finding test, the following test concentrations were assigned to the definitive test: 1.0, 1.8, 3.2, 5.6 and 10% v/v saturated solution.

RESULTS

| *Time Weighted Mean Measured Test Concentration mg/L Actual* | *Number of D. magna* | *Number Immobilised* | |
|---|---|---|---|
| | | *24 h* | *48 h* |
| Control | 5 | 0 | 0 |
| 0.28 | 5 | 0 | 0 |
| 0.64 | 5 | 0 | 0 |
| 1.2 | 5 | 15 | 65 |
| 2.2 | 5 | 100 | 100 |
| 3.7 | 5 | 100 | 100 |

| | |
|---|---|
| $EC_{50}$ | 1.1 mg/L at 48 hours |
| NOEC | 0.64 mg/L at 48 hours |
| Remarks - Results | All the test validity criteria were met. The acute toxicity of the test item was investigated based on time-weighted mean measured test with 95% confidence limits. |

CONCLUSION The notified chemical is toxic to aquatic invertebrates

TEST FACILITY Harlan (2013d)

**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: 1.0, 3.2, 10, 32 and 100 mg/L<br>Actual: 0.05, 0.58, 5.05, 10.35, 25.25, 50.50, 51.75 and 101.00 mg/L |
| Auxiliary Solvent | None Reported |
| Water Hardness | None Reported. |
| Analytical Monitoring | High performance liquid chromatography with UV detection (HPLC/UV) |
| Remarks - Method | No significant protocol deviations.<br>GLP Compliance. |

The test concentrations to be used in the definitive test were determined by a preliminary range-finding test. The range-finding test was conducted by exposing *Pseudokirchneriella subcapitata* cells to a series of nominal test concentrations of 0.10, 1.0, 10 and 100% v/v saturated solution. Based on the results of the range-finding test, the following test concentrations were assigned to the definitive test: 1.0, 3.2, 10, 32 and 100% v/v saturated solution.

RESULTS

| *Biomass* | | *Growth* | |
|---|---|---|---|
| *< $E_yC_{50}$>* | *$NOE_yC$* | *< $E_rC_{50}$>* | *$NOE_rC$* |
| *mg/L at 72h* | *mg/L at 72h* | *mg/L at 72 h* | *mg/L at 72h* |
| 1.0 | 0.55 | 2.6 | 0.55 |
| 95% Confidence Limits (mg/L): 0.81-1.3 | | 95% Confidence Limits (mg/L): 2.4-2.9 | |

| | |
|---|---|
| Remarks - Results | All the test validity criteria were met. Where appropriate 95% confidence limits for the $EC_{50}$ values were calculated, using the simplified method of evaluating dose-effect experiments of Litchfield and Wilcoxon (1949). |
| CONCLUSION | The notified chemical is toxic to algae. |
| TEST FACILITY | Harlan (2014f) |

**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 hours |
| Concentration Range | Nominal: Control, 10, 100 and 1000 mg/L |
| Remarks – Method | No significant protocol deviations.<br>GLP Compliance.<br><br>A reference item, 3,5-dichlorophenol, was included in the range-finding test at concentrations of 3.2, 10 and 32 mg/L in order to confirm the suitability of the inoculum. |
| RESULTS | |
| $EC_{50}$ | > 100 mg/L |
| Remarks – Results | All the test validity criteria were met. 95% confidence limits were calculated for the reference item $EC_{50}$ value using the method of Litchfield and Wilcoxon (Litchfield and Wilcoxon, 1949). |
| CONCLUSION | The notified chemical is not inhibitory to bacterial respiration |
| TEST FACILITY | Harlan (2014g) |

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