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August 2020

**AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME  
(AICIS)**

**PUBLIC REPORT**

**Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate**

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019 (the IC Act)* and *Industrial Chemicals (General) Rules 2019 (the IC Rules)* by following the *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019 (the Transitional Act)* and *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019 (the Transitional Rules)*. The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) 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 Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the AICIS website. For enquiries please contact AICIS at:

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**Executive Director  
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## SUMMARY

The following details will be published on our website:

| ASSESSMENT REFERENCE | APPLICANT(S)      | CHEMICAL OR TRADE NAME                                      | HAZARDOUS CHEMICAL | INTRODUCTION VOLUME | USE                  |
|----------------------|-------------------|---|--------------------|---------------------|----------------------|
| LTD/1791             | Firmenich Pty Ltd | Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate | Yes                | ≤ 1 tonne per annum | Fragrance ingredient |

## CONCLUSIONS AND REGULATORY OBLIGATIONS

### Hazard Classification

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

| <i>Hazard Classification</i>     | <i>Hazard Statement</i>                    |
|----------------------------------|--|
| Skin Sensitisation (Category 1B) | H317 - May cause an allergic skin reaction |

### Human Health Risk Assessment

Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

When used at a maximum concentration of 0.5% in fine fragrances and household products (including air fresheners) and 0.1% in other cosmetics, the assessed chemical is not considered to pose an unreasonable risk to public health.

### Environmental Risk Assessment

On the basis of the maximum import volume of one tonne per annum, the assessed chemical is not considered to pose an unreasonable risk to the environment.

### Recommendations

#### REGULATORY CONTROLS

#### Hazard Classification and Labelling

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

The above should be used for products/mixtures containing the assessed chemical, if applicable, based on the concentration of the assessed chemical present.

#### Health Surveillance

- As the assessed chemical is a skin sensitizer, 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 assessed chemical during reformulation:
  - Enclosed/automated processes, where possible
  - Local exhaust ventilation and/or appropriate extraction systems, where possible
- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the assessed chemical during reformulation:
  - Avoid contact with skin and eyes
  - Avoid inhalation of aerosols or mists
- 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 assessed chemical during reformulation:
  - Protective clothing
  - Impervious gloves
  - Respiratory protection if inhalation exposure may occur

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

- A copy of the SDS should be easily accessible to employees.
- If products and mixtures containing the assessed chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of 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.

### Storage

- The handling and storage of the assessed 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 assessed chemical should be handled by physical containment, collection and subsequent safe disposal.

### Disposal

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

## Regulatory Obligations

### *Specific Requirements to Provide Information*

This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under Section 101 of the IC Act the applicant of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if:

- the importation volume exceeds one tonne per annum assessed chemical;
- the final use concentration of the assessed chemical exceeds 0.5% in fine fragrances and household products (including air fresheners), and 0.1% in other cosmetics;
- the function or use of the chemical has changed from a fragrance ingredient or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

*Safety Data Sheet*

The SDS of the assessed chemical provided by the applicant was reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

## ASSESSMENT DETAILS

### 1. APPLICANT AND APPLICATION DETAILS

#### APPLICANT(S)

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

#### APPLICATION CATEGORY

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

#### PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)

Data items and details taken to be protected information include: other names, analytical data, degree of purity, impurities, additives/adjuvants and use details.

#### VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)

Schedule data requirements are varied for adsorption/desorption, dissociation constant, flammability, explosive properties and oxidising properties.

#### PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)

None

#### APPLICATION IN OTHER COUNTRIES

EU (2004), USA (2005), Philippines (2006), Switzerland (2006), Japan (2007)

### 2. IDENTITY OF CHEMICAL

#### MARKETING NAME

Acetarolle

#### CAS NUMBER

678981-31-2

#### CHEMICAL NAME

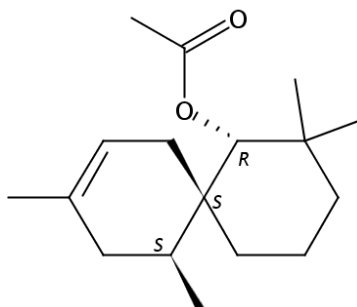
Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate

#### MOLECULAR FORMULA

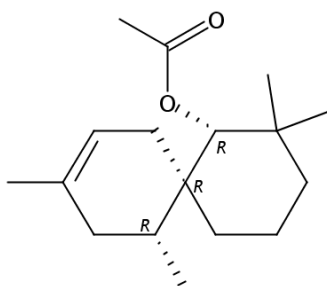
C<sub>17</sub>H<sub>28</sub>O<sub>2</sub>

#### STRUCTURAL FORMULA

The assessed chemical consists of two diastereoisomers:



Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate, (1*R*,6*S*,11*S*)-*rel*- (CAS No. 678981-46-9)



Spiro[5.5]undec-8-en-1-ol, 2,2,9,11-tetramethyl-, 1-acetate, (1R,6R,11R)-rel- (CAS No. 678981-47-0)

#### MOLECULAR WEIGHT

264.40 g/mol

#### ANALYTICAL DATA

Reference <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, FTIR, GC-FID, GC-MS and UV-Vis spectra were provided.

### 3. COMPOSITION

#### DEGREE OF PURITY

> 90%

### 4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: colourless liquid

| <i>Property</i>                         | <i>Value</i>                                     | <i>Data Source/Justification</i>                                    |
|---|--|---|
| Freezing Point                          | < -20 °C   | Measured  |
| Boiling Point                           | 297.5 °C at 97.6 kPa                             | Measured  |
| Density                                 | 996 kg/m <sup>3</sup> at 20 °C                   | Measured  |
| Vapour Pressure                         | 5.3 × 10 <sup>-4</sup> kPa at 25 °C              | Measured  |
| Water Solubility                        | 1.31 × 10 <sup>-3</sup> g/L at 20 °C             | Measured  |
| Hydrolysis as a Function of pH          | Hydrolytically stable at 40 °C (pH 2-12, 5 days) | Measured  |
| Partition Coefficient (n-octanol/water) | log Pow > 6.2 at 30 °C                           | Measured  |
| Adsorption/Desorption                   | log K <sub>oc</sub> = 4.29                       | Calculated using KOCWIN (v 2.0) (US EPA, 2012)                      |
| Dissociation Constant                   | Not determined                                   | Contains no dissociable functionality                               |
| Flash Point                             | 140 °C at 101.3 kPa                              | Measured  |
| Flammability                            | Combustible liquid                               | Based on flashpoint   |
| Autoignition Temperature                | > 220 °C at 97.1 kPa                             | 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 details of tests on physical and chemical properties, refer to Appendix A.

#### *Reactivity*

The assessed 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 assessed 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.

The assessed chemical has a flash point of 140 °C which is greater than 93 °C. Based on *Australian Standard AS1940* definitions for combustible liquid, the assessed chemical may be considered as a Class C2 combustible liquid if the chemical has a fire point below the boiling point.

## 5. INTRODUCTION AND USE INFORMATION

### MODE OF INTRODUCTION OF ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS

The assessed chemical will not be manufactured in Australia. The assessed chemical will be imported into Australia neat or as a component of fragrance formulations at  $\leq 10\%$  concentration, or in finished consumer products at  $\leq 0.5\%$  concentration.

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

| <i>Year</i>   | <i>1</i> | <i>2</i> | <i>3</i> | <i>4</i> | <i>5</i> |
|---------------|----------|----------|----------|----------|----------|
| <i>Tonnes</i> | $\leq 1$ | $\leq 1$ | $\leq 1$ | $\leq 1$ | $\leq 1$ |

### PORT OF ENTRY

Sydney

### IDENTITY OF MANUFACTURER/RECIPIENTS

Firmenich Pty Ltd

### TRANSPORTATION AND PACKAGING

The assessed chemical will be imported in neat form or as a component of fragrance formulations (at  $\leq 10\%$  concentration) in 5-180 kg closed lacquered drums. Within Australia, the drums will be transported from the port of entry by road to the applicant's warehouse facilities for storage and then distributed to industrial customers by road for reformulation. The assessed chemical may also be transported by road to the reformulation sites direct from the port of entry.

The assessed chemical may also be imported in finished consumer products at  $\leq 0.5\%$  concentration and transported by road to retail stores.

### USE

The assessed chemical will be used as a fragrance ingredient at  $\leq 0.5\%$  in fine fragrances and household products (including air fresheners), and  $\leq 0.1\%$  in other cosmetics.

### OPERATION DESCRIPTION

Reformulation of the assessed chemical or fragrance formulations (containing the assessed chemical at  $\leq 10\%$  concentration) into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes will involve blending operations that are highly automated and occur in fully enclosed/contained environments, followed by automated filling of the reformulated end-use products into containers of various sizes.

Consumers and professionals such as hairdressers, beauticians or cleaners will use the assessed chemical at  $\leq 0.5\%$  in fine fragrances and household products, and  $\leq 0.1\%$  in other cosmetics. 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

| <i>Category of Worker</i>     | <i>Exposure Duration<br/>(hours/day)</i> | <i>Exposure Frequency<br/>(days/year)</i> |
|-------------------------------|--|---|
| Transport and storage workers | Not specified                            | Not specified                             |
| Mixer                         | 4  | 2   |
| Drum handling                 | 4  | 2   |



|                        |               |               |
|------------------------|---------------|---------------|
| Drum cleaning          | 4             | 2             |
| Maintenance            | 4             | 2             |
| Quality control        | 0.5           | 2             |
| Packaging              | 4             | 2             |
| Professional end users | Not specified | Not specified |

## EXPOSURE DETAILS

*Transport and storage*

Transport and storage workers may come into contact with the assessed chemical in neat form, as a component of fragrance formulations at  $\leq 10\%$  concentration or in finished consumer products at  $\leq 0.5\%$  concentration, only in the unlikely event of accidental rupture of containers.

*Reformulation workers*

During reformulation, dermal, ocular and inhalation exposure of workers to the assessed chemical at  $\leq 100\%$  concentration may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The applicant states that exposure is expected to be minimised through the use of automated and/or enclosed processes, local exhaust ventilation and through the use of personal protective equipment (PPE) by workers such as protective clothing, eye protection, impervious gloves and respiratory protection.

*Professional end users*

Exposure to the assessed chemical in end-use products (at  $\leq 0.5\%$  concentration in fine fragrances and  $\leq 0.1\%$  concentration in other cosmetics) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers and workers in beauty salons). Exposure to the assessed chemical at  $\leq 0.5\%$  concentration in end-use products may also occur in professions where the services provided involve the use of household products in the cleaning industry. The principal route of exposure will be dermal, whilst ocular and inhalation exposure (e.g. spray products) are 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 the products containing the assessed chemical.

**6.1.2. Public Exposure**

There will be widespread and repeated exposure of the public to the assessed chemical through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure may also occur, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the assessed chemical may be used are shown in the following tables and these are based on information provided in various literature (Cadby *et al.*, 2002; Loretz *et al.*, 2006; ACI, 2010; SCCS, 2012;). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 100% was assumed for the assessed chemical for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Earnest, Jr, 2009; Rothe *et al.*, 2011; Steiling *et al.*, 2014). An adult inhalation rate of 20 m<sup>3</sup>/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%. A lifetime average female body weight (BW) of 70 kg (enHealth, 2012) was used for calculation purposes.

*Cosmetic products (Dermal exposure):*

| Product type          | Amount (mg/day) | C (%) | RF (unitless) | Daily systemic exposure (mg/kg bw/day) |
|-----------------------|-----------------|-------|---------------|--|
| Body lotion           | 7820            | 0.10  | 1             | 0.1117                                 |
| Face cream            | 1540            | 0.10  | 1             | 0.0220                                 |
| Hand cream            | 2160            | 0.10  | 1             | 0.0309                                 |
| Fine fragrances       | 750             | 0.50  | 1             | 0.0536                                 |
| Deodorant (non-spray) | 1500            | 0.10  | 1             | 0.0214                                 |
| Shampoo               | 10460           | 0.10  | 0.01          | 0.0015                                 |
| Conditioner           | 3920            | 0.10  | 0.01          | 0.0006                                 |
| Shower gel            | 18670           | 0.10  | 0.01          | 0.0027                                 |
| Hand wash soap        | 20000           | 0.10  | 0.01          | 0.0029                                 |
| Hair styling products | 4000            | 0.10  | 0.1           | 0.0057                                 |
| <b>Total</b>          |                 |       |               | <b>0.2529</b>                          |

C = maximum proposed concentration of assessed chemical; RF = retention factor.

Daily systemic exposure = (Amount × C × RF × DA)/BW

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

| Product type    | Amount (g/use) | C (%) | Product Retained (PR) (%) | Percent Transfer (PT) (%) | Daily systemic exposure (mg/kg bw/day) |
|-----------------|----------------|-------|---------------------------|---------------------------|--|
| Laundry liquid  | 230            | 0.5   | 0.95                      | 10                        | 0.0156                                 |
| Fabric softener | 90             | 0.5   | 0.95                      | 10                        | 0.0061                                 |
| <b>Total</b>    |                |       |                           |                           | <b>0.0217</b>                          |

C = maximum proposed concentration of assessed chemical

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

*Household products (Direct dermal exposure):*

| Product type        | Frequency (use/day) | C (%) | Contact Area (cm <sup>2</sup> ) | Product Use C (g/cm <sup>3</sup> ) | Film Thickness (cm) | Time Scale Factor | Daily systemic exposure (mg/kg bw/day) |
|---------------------|---------------------|-------|---------------------------------|------------------------------------|---------------------|-------------------|--|
| Laundry liquid      | 1.43                | 0.5   | 1980                            | 0.01                               | 0.01                | 0.007             | 0.0001                                 |
| Dishwashing liquid  | 3                   | 0.5   | 1980                            | 0.009                              | 0.01                | 0.03              | 0.0011                                 |
| All-purpose cleaner | 1                   | 0.5   | 1980                            | 1                                  | 0.01                | 0.007             | 0.0099                                 |
| <b>Total</b>        |                     |       |                                 |                                    |                     |                   | <b>0.0112</b>                          |

C = maximum proposed concentration of assessed chemical

Daily systemic exposure = (Frequency × C × Contact area × Product Use C × Film Thickness on skin × Time Scale Factor × DA)/BW

*Hairspray (Inhalation exposure):*

| Product type | Amount (g/use) | C (%) | Inhalation rate (m <sup>3</sup> /day) | Exposure duration zone 1 (min) | Exposure duration zone 2 (min) | Fraction inhaled (%) | Volume zone 1 (m <sup>3</sup> ) | Volume zone 2 (m <sup>3</sup> ) | Daily systemic exposure (mg/kg bw/day) |
|--------------|----------------|-------|---------------------------------------|--------------------------------|--------------------------------|----------------------|---------------------------------|---------------------------------|--|
| Hairspray    | 9.89           | 0.1   | 20                                    | 1                              | 20                             | 50                   | 1                               | 10                              | <b>0.0029</b>                          |

C = maximum proposed concentration of assessed chemical

Total daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × BW)]

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 assessed chemical at the maximum intended concentrations specified by the applicant in various product types. This would result in a combined internal dose of 0.2887 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, the combination of the conservative hair spray inhalation exposure assessment parameters used and the aggregate exposure from use of the dermally applied products (using a conservative 100% dermal absorption rate), are sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray cosmetic and household products containing it with low exposure (e.g. air fresheners).

## 6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the assessed chemical, an analogue chemical, and its metabolite are summarised in the following table. For details of the studies on the assessed chemical, refer to Appendix B.

| Endpoint  | Result and Assessment Conclusion                                    |
|---|---|
| Acute oral toxicity – rat                         | LD50 > 2000 mg/kg bw; low toxicity                                  |
| Skin irritation – rabbit                          | slightly irritating   |
| Eye irritation – rabbit                           | slightly irritating   |
| Skin sensitisation – mouse local lymph node assay | evidence of sensitisation (EC3 = 20.5%)                             |
| Skin sensitisation – HRIPT                        | no evidence of sensitisation at maximum tested concentration of 10% |
| Repeat dose oral toxicity – rat, 28 days*         | NOAEL = 50 mg/kg bw/day   |
| Mutagenicity – bacterial reverse mutation         | non mutagenic   |

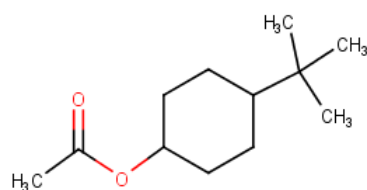
| <i>Endpoint</i>  | <i>Result and Assessment Conclusion</i>               |
|--|---|
| Reproductive and developmental toxicity – rat, 14 days** | NOAEL (maternal and developmental) = 160 mg/kg bw/day |

\*From a study summary for a metabolite (4-*tert*-butylcyclohexanol, CAS No. 98-52-2) of an analogue chemical (Belsito *et al.*, 2008).

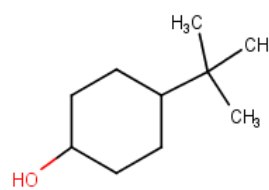
\*\*From a study summary for an analogue chemical (4-*tert*-butylcyclohexyl acetate, CAS No. 32210-23-4) (Belsito *et al.*, 2008).

The assessed chemical and the analogue chemical, 4-*tert*-butylcyclohexyl acetate, are both considered as cyclic acetates. Both have similar molecular weights (264.4 g/mol and 198.3 g/mol, respectively) and share biologically relevant structural elements.

In humans, cyclic acetates are assumed to be rapidly hydrolysed to their corresponding alcohols and carboxylic acids. As such, 4-*tert*-butylcyclohexanol is considered a metabolite of 4-*tert*-butylcyclohexyl acetate (Belsito *et al.*, 2008).



4-*tert*-Butylcyclohexyl acetate



4-*tert*-Butylcyclohexanol

#### *Toxicokinetics*

No information on the toxicokinetics of the assessed chemical was provided. Given the low molecular weight of the assessed chemical (264.4 g/mol), absorption across biological membranes may occur. However dermal absorption may be limited based on its low water solubility ( $1.31 \times 10^{-3}$  g/L at 20 °C) and high partition coefficient ( $\log P_{ow} > 6.2$  at 30 °C).

#### *Acute Toxicity*

The assessed chemical was of low acute oral toxicity in rats. No acute dermal or inhalation toxicity data were provided for the assessed chemical.

#### *Irritation and Sensitisation*

In a skin irritation study in rabbits, slight erythema was observed in all test animals. However, all signs of irritation were resolved at the 48 hour observation.

In an eye irritation study in rabbits, mild to moderate conjunctival irritation was noted. However, all signs of irritation were resolved at the 72 hour observation.

The assessed chemical was found to be a weak skin sensitiser in a mouse local lymph node assay (LLNA), with an EC<sub>3</sub> value of 20.5%.

The assessed chemical was not found to be a skin sensitiser in a human repeat insult patch test (HRIPT) when tested at 10% concentration.

#### *Repeated Dose Toxicity*

The Belsito *et al.* (2008) review article “A toxicologic and dermatologic assessment of cyclic acetates when used as fragrance ingredients” summarises safety data relating to assessing the risk associated with the use of some cyclic acetates as fragrance ingredients. The review contains a summary of a 28-day repeated dose oral toxicity study in rats conducted with 4-*tert*-butylcyclohexanol (CAS No. 98-52-2) at 0, 50, 150 and 300 mg/kg bw/day. This chemical is considered a metabolite of the analogue chemical in humans. The No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in males and females, based on clinical observations (convulsions, squatting position, straub tail and vocalisation) at higher tested doses (Belsito *et al.*, 2008).

#### *Mutagenicity*

The assessed chemical was non-mutagenic in a bacterial reverse mutation assay.

No genotoxicity test data was supplied.

#### *Toxicity for Reproduction*

No reproductive toxicity data was provided for the assessed chemical.

In a study summary for the analogue chemical, 4-*tert*-butylcyclohexyl acetate (CAS No. 32210-23-4), pregnant rats were dosed via oral gavage at 0, 40, 160, or 640 mg/kg bw/day on gestational days 7-20. The maternal NOAEL was established as 160 mg/kg bw/day. This was based on one rat in the high-dose group displaying adverse clinical observations (decreased motor activity, excess salivation, apparent dehydration; sacrificed on day 20) and all rats in the high-dose group presenting with sparse hair on the limbs, red perioral substance, reduced body-weight gains (entire treatment period) and significantly reduced absolute and relative feed consumption (entire treatment period) (Belsito et al., 2008).

The developmental NOAEL was established as 160 mg/kg bw/day. This was based on transient retardations in the offspring during foetal development. They included significant reductions in foetal body weight and associated significant increases in moderate dilation of the renal pelvis, delayed ossification of the caudal vertebrae, fore- and hind-limb phalanges and hind-limb metatarsals (Belsito *et al.*, 2008).

#### **Health Hazard Classification**

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

| <i>Hazard Classification</i>     | <i>Hazard Statement</i>                    |
|----------------------------------|--|
| Skin sensitisation (Category 1B) | H317 – May cause an allergic skin reaction |

### **6.3. Human Health Risk Characterisation**

#### **6.3.1. Occupational Health and Safety**

Based on the toxicological information provided and available data, the assessed chemical is a weak skin sensitiser. It is also slightly irritating to the skin and eyes.

#### *Reformulation*

Workers may experience dermal, ocular and perhaps inhalation exposure to the assessed chemical at  $\leq 100\%$  concentration during reformulation. Given the assessed chemical is a skin sensitiser, caution should be exercised when handling the assessed chemical during reformulation processes.

Provided that control measures are in place to minimise worker exposure, including the use of enclosed, automated processes and PPE such as protective clothing, impervious gloves and respiratory protection (if inhalation exposure may occur), the risk to the health of workers during the handling of the assessed chemical is not considered to be unreasonable.

#### *End-use*

Cleaners and beauty care professionals will handle the assessed chemical at  $\leq 0.5\%$  concentration in fine fragrances and household products, and at  $\leq 0.1\%$  concentration in other cosmetics, similar to public use. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the assessed chemical is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2 below.

#### **6.3.2. Public Health**

Members of the public may experience repeated exposure to the assessed chemical through use of the assessed chemical at  $\leq 0.5\%$  in fine fragrances and household products, and  $\leq 0.1\%$  in other cosmetics.

#### *Sensitisation*

Based on the results of an LLNA, the assessed chemical is a weak skin sensitiser with an EC3 value of 20.5%. When tested in a HRIPT at 10% concentration, the assessed chemical was non-sensitising.

Using fine fragrances which contain the assessed chemical at  $\leq 0.5\%$  concentration as a worst-case example of leave-on cosmetic products containing the assessed chemical, the Consumer Exposure Level (CEL) is estimated

to be 18.75 µg/cm<sup>2</sup>/day. Consideration of the HRIPT study details and application of appropriate safety factors, an Acceptable Exposure Level (AEL) of 49.80 µg/cm<sup>2</sup>/day is estimated for the assessed chemical. In this instance, the factors employed in the estimation included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 100. The availability of additional information on the sensitisation potential of the assessed chemical (i.e., the LLNA study) was taken into account when determining the safety factors.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the assessed chemical in fine fragrances at ≤ 0.5% concentration (a worst-case example of leave-on cosmetic products containing the assessed chemical) is not considered to be unreasonable. Based on the lower expected exposure levels from other cosmetic and household products containing the assessed chemical, by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. However, it is acknowledged that consumers may be exposed to multiple products containing the assessed chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

#### *Repeated dose toxicity*

The repeat dose toxicity potential was estimated based on the margin of exposure (MoE).

Using the worst case exposure scenario from use of multiple products, a total exposure of 0.2887 mg/kg bw/day (see Section 6.1.2) was derived. Using a NOAEL of 50 mg/kg bw/day for the assessed chemical (derived from a 28 day repeated dose oral toxicity study in rats with a metabolite of an analogue chemical), the margin of exposure (MoE) was estimated to be 173. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Overall, based on the information available, the risk to the public associated with use of the assessed chemical at ≤ 0.5% concentration in fine fragrances and household products (including air fresheners), and at ≤ 0.1% concentration in other cosmetics, 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 assessed chemical will be imported into Australia as a component of finished cosmetic and household products, or imported neat or as a component of fragrance oils for reformulation into cosmetic and household products. In general, reformulation processes are expected to involve automated blending operations in an enclosed environment, followed by automated filling of finished products into end-use containers. Wastewater generated from reformulation equipment cleaning is expected to be reused for new purposes. Empty import containers will be either recycled or disposed of through an approved waste management facility. Accidental spills or leaks of the assessed chemical is expected to be collected for disposal, in accordance with local government regulations.

##### RELEASE OF CHEMICAL FROM USE

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

##### RELEASE OF CHEMICAL FROM DISPOSAL

Residues of the assessed chemical in empty end-use containers are either recycled or disposed of to landfill, in accordance with local government regulations. The applicant estimates that 3% of the end use products (containing the assessed chemical at ≤ 0.5% concentration) will remain in empty end use containers.

#### **7.1.2. Environmental Fate**

Following its use in cosmetic and household products, the majority of the assessed chemical will enter the sewers and be treated at sewage treatment plants (STPs) before potential release to surface waters nationwide. A proportion of the assessed chemical may volatilise to air. The half-life of the assessed chemical in air is calculated to be 1.26 hours reaction with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). Therefore, the assessed chemical is not expected to persist in the air compartment.

A ready biodegradation test conducted on the assessed chemical indicates that it is not readily biodegradable (9% degradation over 28 days). However, the ready biodegradability tests (OECD 301 series A-F) are stringent screening tests and chemicals which pass the thresholds will almost invariably biodegrade rapidly and completely. Failure to pass these requirements of these studies does not automatically mean that a chemical is unlikely to biodegrade in the environment. The main reasons for this, are that the detection methods are indirect and do not provide information on any intermediate breakdown products and the inoculum only represents a tiny fraction of the organisms which may degrade chemicals in the environment (Boethling & Mackay, 2000). Although the assessed chemical is not readily biodegradable, it contains an ester functionality which has a common microbial degradation pathway (*ibid*). The results of the ready biodegradation study supports this premise as degradation was initially slow with a rapid increase before termination. Therefore the assessed chemical is unlikely to be persistent in the environment. For details of the biodegradation study, refer to Appendix C.

The assessed chemical is expected to highly sorb to sludge at STPs based on its low water solubility and high partition coefficient ( $\log P_{ow} > 6.2$ ). Therefore, the assessed chemical is expected to be removed effectively at STPs through biodegradation and adsorption to sludge, and only a small portion of the assessed chemical may be released to surface waters. A proportion of the assessed chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation or disposed of to landfill. The assessed chemical as residues in landfill and soils is expected to have very low mobility based on its soil adsorption coefficient ( $\log K_{oc} = 4.29$ ).

The assessed chemical has bioaccumulation potential based on its octanol-water partition coefficient value ( $\log P_{ow} > 6.2$ ) and lack of ready biodegradability. However, overall the assessed chemical is not expected to be persistent in the environment and is therefore unlikely to bioaccumulate. In the aquatic and soil compartments, the assessed chemical is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

### 7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the assessed chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the assessed chemical into sewer systems nationwide over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes based on the properties of the assessed chemical has not been considered for this scenario, and therefore no removal of the assessed chemical during sewage treatment processes is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

| Predicted Environmental Concentration (PEC) for the Aquatic Compartment |        |                   |
|---|--------|-------------------|
| Total Annual Import/Manufactured Volume                                 | 1,000  | kg/year           |
| Proportion expected to be released to sewer                             | 100%   |                   |
| Annual quantity of chemical released to sewer                           | 1,000  | kg/year           |
| Days per year where release occurs                                      | 365    | days/year         |
| Daily chemical release:   | 2.74   | kg/day            |
| Water use   | 200.0  | L/person/day      |
| Population of Australia (Millions)                                      | 24.386 | million           |
| Removal within STP  | 0%     | <b>Mitigation</b> |
| Daily effluent production:  | 4,877  | ML                |
| Dilution Factor - River   | 1.0    |                   |
| Dilution Factor - Ocean   | 10.0   |                   |
| PEC - River:  | 0.56   | 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 1,000 L/m<sup>2</sup>/year (10 ML/ha/year). The assessed chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1,500 kg/m<sup>3</sup>). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.75 µg/kg.

## 7.2. Environmental Effects Assessment

No ecotoxicity data were submitted.

**7.2.1. Predicted No-Effect Concentration**

The Predicted No-Effect Concentration (PNEC) was not calculated as no ecotoxicity data were submitted.

**7.3. Environmental Risk Assessment**

The Risk Quotient (PEC/PNEC) was not calculated as no ecotoxicity data were submitted. The assessed chemical undergoes inherent degradation and is therefore unlikely to be persistent in the environment. On the basis of the maximum import volume of one tonne per annum, the assessed chemical is not considered to pose an unreasonable risk to the environment.

**APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES**

|  |  |
|--|--|
| <b>Freezing Point</b>                          | < - 20 °C  |
| Method   | OECD TG 102 Melting Point/Melting Range (1995)<br>Commission Directive 92/69/EEC A.1 Melting/Freezing Temperature (1992)   |
| Remarks  | Freezing temperature measured in a dry ice/isopropanol bath  |
| Test Facility                                  | Firmenich (2003a)  |
| <b>Boiling Point</b>                           | 297.5 °C at 97.6 kPa   |
| Method   | OECD TG 103 Boiling Point (1995)<br>Commission Directive 92/69/EEC A.2 Boiling Temperature (1992)  |
| Remarks  | Determined by Siwoloboff method  |
| Test Facility                                  | Firmenich (2003a)  |
| <b>Density</b>                                 | 996 kg/m <sup>3</sup> at 20 °C   |
| Method   | OECD TG 109 Density of Liquids and Solids (1995)<br>Commission Directive 92/69/EEC A.3 Relative Density (1992)   |
| Remarks  | Determined by oscillating density meter  |
| Test Facility                                  | Firmenich (2003a)  |
| <b>Vapour Pressure</b>                         | 5.3 × 10 <sup>-4</sup> kPa at 25 °C  |
| Method   | OECD TG 104 Vapour Pressure (1995)   |
| Remarks  | Determined using dynamic measurement   |
| Test Facility                                  | Firmenich (2003b)  |
| <b>Water Solubility</b>                        | 1.31 x 10 <sup>-3</sup> 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. The concentration of the test substance was analysed by High Performance Liquid Chromatography (HPLC).   |
| Test Facility                                  | SafePharm (2003a)  |
| <b>Hydrolysis as a Function of pH</b>          | Hydrolytically stable at 40 °C   |
| Method   | Internal method: the test substance was dissolved in pH buffers containing surfactant and stored at 40 °C. Small aliquots of the test solution were extracted with an organic solvent containing a hydrocarbon standard at 0, 0.25, 1, 2, 4, 7, 15, 21 and 28 days throughout the test. The extracts were analysed by gas chromatography-flame ionisation detector (GC-FID). |
| Remarks  | The test substance was found hydrolytically stable at pH 2, 5, 7, 8.5, 12 and 40 °C.   |
| Test Facility                                  | Firmenich (2014)   |
| <b>Partition Coefficient (n-octanol/water)</b> | log Pow = > 6.2 at 30 °C   |
| Method   | OECD TG 117 Partition Coefficient (n-octanol/water).<br>EC Council Regulation No 440/2008 A.8 Partition Coefficient.   |
| Remarks  | HPLC Method; the column temperature was 30 °C.   |
| Test Facility                                  | SafePharm (2003a)  |
| <b>Flash Point</b>                             | 140 °C at 101.3 kPa  |
| Method   | Commission Directive 92/69/EEC A.9 Flash Point (1992)  |
| Remarks  | Closed cup method  |
| Test Facility                                  | Firmenich (2003a)  |



**Autoignition Temperature** > 220 °C at 97.1 kPa

|               |   |
|---------------|---|
| Method        | Similar to EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases) |
| Remarks       | Test conducted up to 220 °C   |
| Test Facility | Firmenich (2003c)   |

**APPENDIX B: TOXICOLOGICAL INVESTIGATIONS****B.1. Acute Oral Toxicity – Rat**

|                  |   |
|------------------|---|
| TEST SUBSTANCE   | Assessed chemical   |
| METHOD           | OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001) |
| Species/Strain   | Rat/ Sprague-Dawley CD  |
| Vehicle          | None  |
| Remarks – Method | No significant protocol deviations                                |

## RESULTS

| Group | Number and Sex of Animals | Dose (mg/kg bw) | Mortality |
|-------|---------------------------|-----------------|-----------|
| 1     | 3F                        | 2000            | 0/3       |
| 2     | 3F                        | 2000            | 0/3       |

|                   |  |
|-------------------|--|
| LD50              | > 2000 mg/kg bw  |
| Signs of Toxicity | There were no unscheduled deaths during the study. No clinical signs of systemic toxicity were observed. |
| Effects in Organs | No abnormalities were recorded at necroscopy.  |
| Remarks – Results | All animals showed expected body weight gains over the study period.                                     |

CONCLUSION The assessed chemical is of low acute toxicity via the oral route.

TEST FACILITY SafePharm (2003b)

**B.2. Skin Irritation – Rabbit**

|                    |   |
|--------------------|---|
| TEST SUBSTANCE     | Assessed chemical   |
| METHOD             | OECD TG 404 Acute Dermal Irritation/Corrosion (1992)<br>EC Directive 92/69/EEC Method B.4 Acute Toxicity (Skin Irritation)  |
| Species/Strain     | Rabbit/New Zealand White  |
| Number of Animals  | 3 male  |
| Vehicle            | None  |
| Observation Period | 72 hours  |
| Type of Dressing   | Semi-occlusive  |
| Remarks – Method   | No significant protocol deviations.<br>After a single 4-hour application on the intact back skin of 3 male rabbits, test sites were assessed for dermal irritation at 1, 24, 48 and 72 hours. |

## RESULTS

| Lesion          | Mean Score* |     |     | Maximum Value | Maximum Duration of Any Effect | Maximum Value at End of Observation Period |
|-----------------|-------------|-----|-----|---------------|--------------------------------|--|
|                 | 1           | 2   | 3   |               |                                |  |
| Erythema/Eschar | 0.3         | 0.3 | 0.3 | 1             | < 48 h                         | 0  |
| Oedema          | 0           | 0   | 0   | 0             | -                              | 0  |

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

Remarks – Results Slight erythema was observed in all test animals at the 1 and 24 hour observations. All observed effects were reversed to normal by 48 hours.

CONCLUSION The assessed chemical is slightly irritating to the skin.

TEST FACILITY SafePharm (2003c)

### B.3. Eye Irritation – Rabbit

TEST SUBSTANCE Assessed chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion (2002)  
EC Directive 92/69/EEC Method B.5 Acute Toxicity (Eye Irritation)

Species/Strain Rabbit/New Zealand White  
Number of Animals 3 male  
Observation Period 72 hours  
Remarks – Method No significant protocol deviations.  
Test sites were assessed for ocular damage/irritation at 1, 24, 48 and 72 hours after administration of the test chemical.

#### RESULTS

| Lesion                 | Mean Score* |   |     | Maximum Value | Maximum Duration of Any Effect | Maximum Value at End of Observation Period |
|------------------------|-------------|---|-----|---------------|--------------------------------|--|
|                        | 1           | 2 | 3   |               |                                |  |
| Conjunctiva: Redness   | 0.3         | 0 | 0.3 | 1             | < 48 h                         | 0  |
| Conjunctiva: Chemosis  | 0           | 0 | 0   | 0             | < 24 h                         | 0  |
| Conjunctiva: Discharge | 0.3         | 0 | 0   | 1             | < 48 h                         | 0  |
| Corneal Opacity        | 0           | 0 | 0   | 0             | -                              | 0  |
| Iridial Inflammation   | 0           | 0 | 0   | 0             | -                              | 0  |

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

Remarks – Results Minimal to moderate conjunctival irritation was noted in all animals 1 hour after treatment. Minimal conjunctival irritation was observed in two animals at the 24 hour observation. All observed effects were reversed to normal by 48 hours. No corneal or iridial effects were observed.

CONCLUSION The assessed chemical is slightly irritating to the eye.

TEST FACILITY SafePharm (2003d)

### B.4. Skin Sensitisation – LLNA

TEST SUBSTANCE Assessed chemical

METHOD In-house protocol (similar to OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010))

Species/Strain Mouse/CBA/J  
Vehicle Acetone:olive oil (4:1)  
Preliminary study No  
Positive control Isoeugenol (conducted in parallel with the test substance).  
Remarks – Method No significant protocol deviations.

No pre-screen test to determine the maximum appropriate test substance concentration was reported.

#### RESULTS

| Concentration (% w/w) | Number and Sex of Animals | Proliferative Response (mean DPM/mouse $\pm$ SD) | Stimulation Index (test/control ratio) |
|-----------------------|---------------------------|--|--|
| <i>Test Substance</i> |                           |  |  |
| 0 (vehicle control)   | 8F                        | 36.7 $\pm$ 15.7                                  |  |
| 1                     | 5F                        | 29.2 $\pm$ 3.6                                   | 0.8                                    |
| 5                     | 5F                        | 36.7 $\pm$ 6.0                                   | 1.0                                    |

|                         |    |               |     |
|-------------------------|----|---------------|-----|
| 10                      | 5F | 46.3 ± 10.6   | 1.3 |
| 20                      | 5F | 118.7 ± 48.4  | 3.2 |
| 40                      | 5F | 266.6 ± 101.2 | 7.3 |
| <i>Positive Control</i> |    |               |     |
| 0.5                     | 5F | 55.7 ± 16.3   | 1.5 |
| 1.0                     | 5F | 85.0 ± 33.4   | 2.3 |
| 5.0                     | 5F | 333.9 ± 125.0 | 9.1 |

|                   |   |
|-------------------|---|
| EC3               | 20.5%   |
| Remarks – Results | <p>No irritation, mortalities, signs of systemic toxicity or effects on body weight were noted in the test animals.</p> <p>The test substance elicited stimulation indices (SI) ≥ 3 at the 20% and 40% concentrations, although only the 40% concentration was statistically significant.</p> <p>The EC potency value for the test substance was determined to be 5,125 µg/cm<sup>2</sup>.</p> <p>The authors of this study noted that mean ear thickness between days 1 and 3 did not increase by 10% or more in any tested animals, and thus primary irritation was not considered a contributing factor in the lymph node proliferation observed in the study.</p> <p>The calculated EC3 and potency value for the positive control (1.32% and 330 µg/cm<sup>2</sup>, respectively) were consistent with previously reported results, thereby confirming the reliability of the test system.</p> |
| CONCLUSION        | There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the assessed chemical.   |
| TEST FACILITY     | BRT (2004)  |

### B.5. Skin Sensitisation – Human Volunteers

|                  |   |
|------------------|---|
| TEST SUBSTANCE   | Assessed chemical (10% in vehicle)  |
| METHOD           | Human repeated insult patch test (HRIPT)  |
| Study Design     | <p>A pilot study was conducted prior to the main study to determine the feasibility of testing the test substance on a larger study population by evaluating the ability of the test substance to sensitise the skin of normal subjects.</p> <p>The pilot study and the main study both consisted of three phases:</p> <ul style="list-style-type: none"> <li>• Induction phase: 9 × 24-hour applications (0.2 mL), grading of responses at 48- or 72-hour intervals over a 3-week period</li> <li>• Rest phase: 10–15 days</li> <li>• Challenge phase: 1 × 24-hour application (0.2 mL) on a naïve site, grading of responses at 48 or 72 hours post patch removal.</li> </ul> <p>Rechallenge was not conducted.</p> |
| Study Groups     | <p>Pilot Study: 16 F, 2 M; age range 29 – 73 years</p> <p>Main Study: 91 F, 23 M; age range 18 – 70 years</p>   |
| Vehicle          | Diethyl phthalate   |
| Remarks – Method | Occluded and semi-occluded. The test substance was spread on a 2 cm × 2 cm patch.   |
| RESULTS          |   |

|                                     |   |
|-------------------------------------|---|
| Remarks – Results                   | <p>Pilot study: 17/18 subjects completed the study (1 subject voluntarily withdrew after the first induction application, before grading could be conducted). No adverse reactions were recorded during the challenge phase. In the pilot study challenge phase, 1/17 subjects exhibited a minimal or doubtful response at 48 and 72 hours.</p> <p>Main study: 100/114 subjects completed the study. Ten applicants were discontinued for failure to keep to the scheduled visits (3-6 induction observations recorded) and four voluntarily withdrew (following the first and second induction readings). A minimal or doubtful response was noted for 1 subject at the first induction grading. No responses were noted during the challenge phase.</p> |
| CONCLUSION                          | The assessed chemical (at 10% concentration) was non-sensitising under the conditions of the test.  |
| TEST FACILITY                       | TKL (2004)  |
| <b>B.6. Genotoxicity – Bacteria</b> |   |
| TEST SUBSTANCE                      | Assessed chemical   |
| METHOD                              | <p>OECD TG 471 Bacterial Reverse Mutation Test<br/>         EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria<br/>         Plate incorporation procedure (48-hour incubation at 37 °C)<br/> <i>Salmonella typhimurium</i>: TA1535, TA100, TA102, TA1537, TA98<br/>         S9 fractions from phenobarbitone/<math>\beta</math>-naphthoflavone induced rat livers</p>  |
| Species/Strain                      |   |
| Metabolic Activation System         |   |
| Concentration Range in Main Test    | a) With metabolic activation: 50–5000 $\mu\text{g}/\text{plate}$<br>b) Without metabolic activation: 50–5000 $\mu\text{g}/\text{plate}$   |
| Vehicle                             | Dimethyl sulfoxide  |

Remarks – Method

No deviations from the test guideline

Preliminary toxicity test: TA100 exposed to ten concentrations of the test substance ranging 0.15–5000 µg/plate, with and without metabolic activation, to select appropriate dose levels for the main study.

Test 1 and 2 of the main study: each strain exposed to five concentrations of test substance, with and without metabolic activation.

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

Positive controls:

- i) with metabolic activation: 2-aminoanthracene (TA100, TA1535, TA1537), 1,8-dihydroxyanthraquinone (TA102), and benzo(a)pyrene (TA98)
- ii) without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine (TA100, TA1535), 9-aminoacridine (TA1537), mitomycin C (TA102) and 4-nitroquinoline-1-oxide (TA98)

## RESULTS

| <i>Metabolic Activation</i> | <i>Test Substance Concentration (µg/plate) Resulting in:</i> |                                  |                      |                         |
|-----------------------------|--|----------------------------------|----------------------|-------------------------|
|                             | <i>Cytotoxicity in Preliminary Test (TA100)</i>              | <i>Cytotoxicity in Main Test</i> | <i>Precipitation</i> | <i>Genotoxic Effect</i> |
| <i>Absent</i>               |  |                                  |                      |                         |
| Test 1                      | > 5000   | > 5000                           | 5000                 | negative                |
| Test 2                      |  | > 5000                           | 5000                 | negative                |
| <i>Present</i>              |  |                                  |                      |                         |
| Test 1                      | > 5000   | > 5000                           | 5000                 | negative                |
| Test 2                      |  | > 5000                           | 5000                 | negative                |

Remarks – Results

In the preliminary toxicity study, the test substance was non-toxic to the TA100 strain at up to 5000 µg/plate, with or without metabolic activation.

The authors of this study noted that an oily precipitate (noted under an inverted microscope only) at 5000 µg/plate would not prevent the scoring of revertant colonies.

No reduction in the growth of the bacterial background was visible at any tested dose levels, with or without metabolic activation.

No significant increases in the frequency of revertant colonies were recorded for any tested strains at up to the maximum dose, with or without metabolic activation.

The positive, negative and vehicle controls gave satisfactory responses, confirming the validity of the test system.

CONCLUSION

The assessed chemical was non-mutagenic to bacteria under the conditions of the test.

TEST FACILITY

SafePharm (2003e)

## APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

### C.1. Environmental Fate

#### C.1.1. Ready Biodegradability

|                       |  |
|-----------------------|--|
| TEST SUBSTANCE        | Assessed chemical  |
| METHOD                | OECD TG 301 B Ready Biodegradability: CO <sub>2</sub> Evolution Test.  |
| Inoculum              | Activated sludge from a sewage treatment plant   |
| Exposure Period       | 28 days  |
| Auxiliary Solvent     | None   |
| Analytical Monitoring | Theoretical Carbon Dioxide (ThCO <sub>2</sub> )  |
| Remarks – Method      | Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. The test substance was poorly soluble in water and therefore it was adsorbed onto an inert support (glass fibre filter paper) prior to dispersion in the test medium in order to increase the surface area to the test organisms. The positive control was sodium benzoate. A toxicity control comprising of the test material adsorbed onto filter paper plus sodium benzoate, was also run. |

#### RESULTS

| <i>Test substance</i> |                      | <i>Sodium benzoate</i> |                      |
|-----------------------|----------------------|------------------------|----------------------|
| <i>Day</i>            | <i>% Degradation</i> | <i>Day</i>             | <i>% Degradation</i> |
| 6                     | 0                    | 6                      | 67                   |
| 14                    | 3                    | 14                     | 78                   |
| 22                    | 0                    | 22                     | 74                   |
| 28                    | 9                    | 28                     | 82                   |

#### Remarks - Results

All validity criteria for the test were satisfied.

The toxicity control attained 28% degradation on day 14 thereby confirming that the assessed chemical was not toxic to the sewage treatment micro-organisms used in the study. The total CO<sub>2</sub> evolution in the control vessels on day 28 was 25.48 mg/L. The difference between values for CO<sub>2</sub> production at the end of the test for the replicate vessels was < 20%.

The test material attained 9% degradation after 28 days and, therefore, cannot be considered as readily biodegradable under the conditions of OECD Guideline 301B.

#### CONCLUSION

The assessed chemical is not readily biodegradable

#### TEST FACILITY

SafePharm (2003f)

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