File No: LTD/2017

June 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Benzeneacetonitrile, α-cyclohexylidene-2-methyl-

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 and Energy.

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

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

Director
NICNAS

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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/2017	Givaudan Singapore Pte Ltd	Benzeneacetonitrile, α-cyclohexylidene-2-methyl-	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 following table.

Hazard classification	*Hazard statement*
Skin sensitisation (Category 1B)	H317 − May cause an allergic skin reaction
Specific target organ toxicity (repeated exposure) (Category 2)	H373 − May cause damage to the heart through prolonged or repeated exposure through the oral route

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of no observed effects to the limits of its water solubility and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin sensitisation (Category 1B): H317 − May cause an allergic skin reaction
  - Specific target organ toxicity (repeated exposure) (Category 2): H373 − May cause damage to the heart through prolonged or repeated exposure through the oral route

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

- 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:
  - Coveralls
  - Impervious gloves

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

- If products and mixtures containing the notified chemical is 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.

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 physical containment, collection and subsequent safe disposal.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 0.23% in fine fragrances, 0.13% in other cosmetic products, 0.42% in fabric care products or 0.01% in household cleaning products;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
Givaudan Singapore Pte Ltd (ABN: 79 368 011 578)
1 Pioneer Turn
SINGAPORE 627576

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Chemical Permit (NICNAS)

NOTIFICATION IN OTHER COUNTRIES
China (2008), EU (2008), Switzerland (2008), USA (2009) and Japan (2012)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Petalia

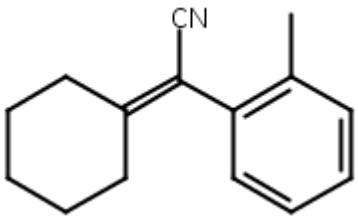
CAS NUMBER
916887-53-1

CHEMICAL NAME
Benzeneacetonitrile, α-cyclohexylidene-2-methyl-

OTHER NAME
α-Cyclohexylidene-2-methylbenzeneacetonitrile

MOLECULAR FORMULA
$C_{15}H_{17}N$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
211.3 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Point	63.4 °C	Measured
Boiling Point	328.9 °C at 101.3 kPa	Measured
Density	1,144 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.8×10^{-5} kPa at 20 °C	Measured
Water Solubility	1.29 ×10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities, but these are unlikely to be susceptible to hydrolysis in the environmentally relevant range (pH 4-9). No accurate determination could be made due to the low solubility of the notified chemical in buffer solutions (pH 4, 7 and 9)
Partition Coefficient (n-octanol/water)	log Pow = 3.45 at 20 °C	Measured.
Surface Tension	61.5 mN/m at 20.7 °C	Measured. Not expected to be surface active
Adsorption/Desorption	log Koc = 3.6 at 35 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Inhalable fraction (< 100 μm): 37.85% Respirable fraction (< 10 μm): 1.88% MMD* = 120.4 μm	Measured
Flash Point	160.3 °C at 100.2 kPa	Measured
Flammability	Not determined	Not expected to be flammable based on measured flash point
Autoignition Temperature	400 °C	Measured
Explosive Properties	Not explosive	Expert statement (provided by the notifier) based on chemical structure
Oxidising Properties	Not oxidising	Expert statement (provided by the notifier) based on chemical structure

*Mass median diameter

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 as a component of fragrance oil mixtures at ≤ 8.5% concentration for reformulation into cosmetic and household products.

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 and Perth

IDENTITY OF RECIPIENTS
Givaudan Pty Ltd

TRANSPORTATION AND PACKAGING
Fragrance oil mixtures containing the notified chemical at ≤ 8.5% concentration will be introduced by sea and air. The mixtures will be packaged in glass, lacquer-lined containers of sizes ranging from 1-190 kg.

Finished products containing the notified chemical at ≤ 0.42% concentration will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products. The proposed maximum use concentration of the notified chemical in various consumer products will be:

Finished Consumer Product	*Maximum Usage Concentration of the Notified Chemical (%)*
Fine fragrance	0.23
Other cosmetic products	0.13
Household cleaning products	0.01
Fabric care	0.42

OPERATION DESCRIPTION

Reformulation
The procedures for reformulating the fragrance oil mixture containing the notified chemical at ≤ 8.5% concentration will vary depending on the nature of the cosmetic and household products, and may involve both automated and manual transfer steps. In general, it is expected that the reformulation processes will involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into consumer containers of various sizes.

End-use
Finished household cleaning products containing the notified chemical at ≤ 0.42% concentration may be used by consumers and professional cleaners. The cleaning products will be generally applied with a cloth or sponge, mop or brush, or by spray followed by wiping. In some cases the cleaning product will be diluted with water prior to application.

The finished cosmetic products containing the notified chemical at ≤ 0.23% 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 and warehouse	None	Incidental
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	4	2
Packaging	4	2
End users (professionals)	1- 8	200

EXPOSURE DETAILS

Transport and storage

Transport, storage and warehouse workers may come into contact with the notified chemical at ≤ 8.5% concentration (in fragrance oil mixtures) or at ≤ 0.42 % concentration (in final formulated products), only in the event of accidental rupture of containers.

Reformulation

During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at ≤ 8.5% concentration may occur during handling of drums, 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 personal protective equipment (PPE) such as protective clothing, eye protection and impervious gloves.

End-use

Exposure to the notified chemical in end-use products at ≤ 0.42% concentration may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hair dressers and 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 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 notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 0.42% concentration) through the use of a wide range of cosmetic and household products. The main route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables and these are based on information provided in various literatures (SCCS, 2016; Cadby et al., 2002; ACI, 2010; Loretz *et al.,* 2006). 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 notified chemical for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%. A lifetime average female body weight (BW) of 64 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	0.13	1	0.1588
Face cream	1540	0.13	1	0.0313
Hand cream	2160	0.13	1	0.0439
Fine fragrances	750	0.23	1	0.0270
Deodorant spray	1430	0.13	1	0.0305
Shampoo	10460	0.13	0.01	0.0021
Conditioner	3920	0.13	0.01	0.0008
Shower gel	18670	0.13	0.01	0.0038
Hand soap	20000	0.13	0.01	0.0041
Hair styling products	4000	0.13	0.1	0.0081
Total				**0.3103**

C = maximum intended concentration of notified 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	0.42	0.95	10	0.0143
Fabric softener	90	0.42	0.95	10	0.0056
Total					**0.0200**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.42	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.01	1980	0.0093	0.01	0.03	0.0000
All-purpose cleaner	1	0.01	1980	1	0.01	0.007	0.0002
Total							**0.0003**

C = maximum intended concentration of notified chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

Hairspray (Inhalation exposure):

Product type	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration zone 1 (min)	Exposure duration zone 2 (min)	Fraction inhaled (%)	Volume zone 1 (m^3)	Volume zone 2 (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.13	20	1	20	50	1	10	**0.0042**

C = maximum intended concentration of notified 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) × body weight)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical at the maximum intended concentrations

specified by the notifier in various product types. This would result in a combined internal dose of 0.3348 mg/kg bw/day for the notified chemical.

It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with low exposures (e.g. air fresheners and deodorants).

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 > 4.076 mg/L/4 hour; low toxicity
Rabbit, skin irritation	not irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay (LLNA)	evidence of sensitisation (EC3 = 9.3%)
Human, skin sensitisation – RIPT	no evidence of sensitisation at 2.5%
Rat, repeat dose gavage toxicity – 28 days.	NOAEL = 50 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic

Toxicokinetics

Given the low molecular weight (211.3 g/mol), the notified chemical may be absorbed across the respiratory or gastrointestinal tract. Based on the low water solubility (1.29×10^{-3} g/L at 20 °C) and high partition coefficient (log Pow = 3.45 at 20 °C), the notified chemical has a reasonably high lipophilicity, and hence percutaneous absorption is expected to be limited.

Acute toxicity

The notified chemical is of low acute oral, dermal and inhalation toxicity based on studies conducted in rats

Irritation and sensitisation

The notified chemical is not irritating to skin and slightly irritating to eyes based on studies conducted in rabbits.

In the eye irritation study, a slight to moderate reddening of the conjunctivae was noted in all animals 1 hour after treatment which persisted as slight to the 72 hour observation. In addition, a slight to moderate reddening of the sclerae was observed in all animals at the 1 hour observation which persisted in one male at the 24 hour observation. At the 7 day observation, all treated eyes appeared normal. No corneal or iridial effects were noted during the study.

The notified chemical was determined to be a skin sensitiser in a mouse local lymph node assay (LLNA) with stimulation indices of 3.2, 5.8 and 8.8 at 10%, 25% and 50%, respectively. The EC3 value (i.e. the estimated concentration of a test substance needed to produce a stimulation index of three) was calculated to be 9.3%. The sensitising potential of the notified chemical was also tested in a human repeat insult patch test (HRIPT). The notified chemical was not a skin sensitiser when tested at 2.5% concentration (with 101 subjects completing the study). No skin reactions were noted in subjects during the induction or challenge phases.

Repeated dose toxicity

In a 28-day repeated dose oral toxicity study in rats, the notified chemical was administered daily by gavage at dose levels of 50, 200, and 1,000 mg/kg bw/day. The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 50 mg/kg bw/day based on myocardial vacuolation in the heart of animals at 200 mg/kg bw/day and 1,000 mg/kg bw/day. As there was no recovery group, the prognosis of this lesion could not be established

Mutagenicity/Genotoxicity
The notified chemical was negative in a bacterial reverse mutation assay and in an *in vitro* chromosomal aberration test in Chinese hamster V79 cells.

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 sensitisation (Category 1B)	H317 − May cause an allergic skin reaction
Specific target organ toxicity (repeated exposure) (Category 2)	H373 − May cause damage to the heart through prolonged or repeated exposure through the oral route

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available toxicological information, the notified chemical is a skin sensitiser and a slight eye irritant. Repeated exposure to the notified chemical at high concentrations may cause severe health effects.

Reformulation
During reformulation, workers may be exposed to the notified chemical introduced at ≤ 8.5% concentration. At this concentration, workers may be at risk of skin sensitisation. According to the notifier engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit worker exposure. Therefore, provided that control measures are in place to minimise worker exposure, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers and beauty salon workers), or the use of household products in the cleaning industry, may be exposed to the notified chemical at ≤ 0.42% concentration. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various products containing the notified chemical.

6.3.2. Public Health
Members of the public will experience widespread and frequent exposure to the notified chemical at ≤ 0.42% concentration through daily use of cosmetic and household cleaning products. The main route of exposure is expected to be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

Sensitisation
Based on the results of an LLNA the notified chemical is a skin sensitiser with an EC3 value of 9.3%. Using fine fragrances as an example for products that may contain the notified chemical (at ≤ 0.23% concentration), as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 8.63 μg/cm^2/day (Cadby *et al*., 2002). Consideration of available information and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 8.87 μg/cm^2/day. In this instance, the factors employed 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.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example of a leave-on cosmetic product) is not considered to be unreasonable. Based on lower expected exposure level from other cosmetic products and household products, 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 notified chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeated dose toxicity
The repeated dose toxicity potential of the notified chemical was estimated by calculation of the margin of exposure (MOE) using the worst case exposure scenario (0.3348 mg/kg bw/day) from use of multiple products containing the notified chemical (see Section 6.1.2) and a NOAEL of 50 mg/kg bw/day, which was established in a 28-day repeated dose oral toxicity study in rats with the notified chemical. The margin of exposure (MOE) was estimated to be 149 for a person using all types of products daily containing the notified chemical. A MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Overall, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.23% in fine fragrances, ≤ 0.13% in other cosmetic products, ≤ 0.42% in fabric care products and ≤ 0.01% in household cleaning products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance formulations for reformulation into finished cosmetic and household products. Significant release of the notified chemical to the environment is not expected from transport and storage, except in the case of accidental spills and leaks. Accidental leaks and spills of the product containing the notified chemical are expected to be collected and disposed of to landfill in accordance with local government regulations.

Wastes containing the notified chemical generated from reformulation including equipment wash water, empty import containers and spilt materials (< 1% of the total import volume as indicated by the notifier) are expected to be disposed to on-site waste water treatment or directly to the sewer system. Empty import containers are expected to be recycled or disposed of through licensed waste management services.

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the aquatic compartments through sewers during its use in various cosmetic formulations and household products.

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated by the notifier that a maximum of 1% of the notified chemical may remain in end-use containers once the consumer products are used up. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to be released to sewers on a nationwide basis after use. In sewage treatment plants (STPs), the notified chemical is not likely to degrade as it is not readily biodegradable. Some of the notified chemical may partition to sludge based on its low water solubility, while some is expected to volatilise based on being moderately volatile (1.80×10^{-2} Pa; according to the classification of Mensink et al. (1995)). Therefore, most of the notified chemical is expected to be released to surface waters with the treated effluent.

In water, the notified chemical is likely to persist as it is shown to be resistant to photolysis and biodegradation. Some loss from surface waters is expected due to volatilisation as indicated by the laboratory-based photolysis study. A proportion of the notified chemical may also partition to sediment based on its low water solubility.

A proportion of the notified chemical may be applied to land when STP effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. The notified chemical is not expected to be very mobile in soil and sludge based on its soil adsorption coefficient (K_{oc}) of 3.6, however losses due to volatilisation are expected from soil.
As volatilisation is possible, the notified chemical is expected to be present in air. However, any notified chemical released to the atmospheric compartment is not expected to persist [atmospheric half-life ($t_{1/2}$) based on reaction with hydroxyl radicals ~ 4.4 hours [AOPWIN v1.92 (US EPA 2012)].

The notified chemical is unlikely to bioaccumulate based on its log Pow of 3.45.

The notified chemical is expected to eventually degrade via biotic and abiotic processes to form water and oxides of carbon and nitrogen.

For the details of the environmental fate studies please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume the worst case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. Based on the its log Pow and moderate volatility, and resistance to biodegradation, it was assumed there will be ~6% removal of the notified chemical during sewage treatment processes, due to partitioning to sludge (~4%) and volatilisation (~2%). The resultant 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:	2.7	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.4	million
Removal within STP	6%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10	
PEC - River:	0.53	µg/L
PEC - Ocean:	0.053	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 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 0.53 µg/L may potentially result in a soil concentration of approximately 3.5 µg/kg. Assuming accumulation in soil under repeated irrigation, the concentration of the notified chemical in applied soil may be approximately 18 µg/kg and 35 µg/kg in 5 and 10 years, respectively.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 0.23 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1,500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.0010 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation in soil under repeated biosolids application, the concentration of the notified chemical in applied soil may approximate 0.0050 mg/kg and 0.010 mg/kg in 5 and 10 years, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 > 1.3 mg/L	Not toxic to the limits of water solubility
Daphnia Toxicity	48 h EC50 > 0.82 mg/L	Not toxic to the limits of water solubility
Algal Toxicity	ErC50 > 1.3 mg/L	Not toxic to the limits of water solubility
Inhibition of Bacterial Respiration	3 h IC50 > 1,000 mg/L	Not inhibitory to microbial respiration.

Based on the acute ecotoxicological endpoints, the notified chemical is not expected to be toxic to aquatic organisms to the limits of its water solubility. Therefore, the notified chemical cannot be classified according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentrations (PNEC) for the notified chemical have not been derived as no effects could be established below the limit of water solubility of the notified chemical.

7.3. Environmental Risk Assessment

The notified chemical is expected to be resistant to degradation. However, no risk quotients were determined for discharge of effluents containing the notified chemical to the aquatic environment as no effects could be established below the limit of water solubility of the notified chemical. In addition, the notified chemical is not likely to bioaccumulate based on its log K_{ow}. In soil, the notified chemical is not expected to be mobile.

Therefore, based on the assessed use pattern in cosmetic formulations and household products, and the no observed toxic effects up to its limit of water solubility, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 63.4 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined using capillary tester
Test Facility	RCC (2008a)

Boiling Point 328.9 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Determined by differential scanning calorimetry
Test Facility	RCC (2008a)

Density 1,144 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Determined using a gas comparison pycnometer.
Test Facility	RCC (2008b)

Vapour Pressure 1.8×10^{-5} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Determined using isothermal thermogravimetric effusion method
Test Facility	NOTOX (2007)

Water Solubility 1.29×10^{-3} g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	The water solubility of the test item was estimated using a simplified flask test to be 1.06×10^{-4} g/L at room temperature. Therefore, the column elution method was used for the performance of the main test. The study was considered valid and no significant deviations from the TG were reported.
Test Facility	RCC (2008c)

Hydrolysis as a Function of pH

Method	OECD TG 111 Hydrolysis as a Function of pH EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH
Remarks	The solubility of test substance (GR-86-6414) in the buffer solutions (pH 4.0, pH 7.0 and pH 9.0) was very low, and hence could not be quantified. Attempts to increase the solubility of the test item were not successful. Therefore, no results could be obtained from the test.
Test Facility	RCC (2008d)

Partition Coefficient (n-octanol/water) log Pow = 3.45 at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method. Test was conducted at room temperature (~20 °C). The log Pow was first determined using six common standards (log Pow = 3.30), but was later determined using eight common standards. The latter log Pow was used for the Assessment. Both studies met the TG quality criteria and no significant deviations from the TG were reported.
Test Facility	RCC (2008c)

Surface Tension 61.5 mN/m at 20.7 °C

Method OECD TG 115 Surface Tension of Aqueous Solutions
EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks Concentration: 90% saturation concentration in water
Test Facility RCC (2008e)

Adsorption/Desorption log K_{oc} = 3.6 at 35 °C

Method OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
EC Council Regulation No 440/2008 C.19 Estimation of the adsorption coefficient (Koc) on soil and on sewage sludge using high performance liquid chromatography (HPLC)
Remarks Results were considered reliable and there were no reported deviations from the TG that are likely to have significantly affected the reliability of the test results. The effects of temperature on the measurement of K_{oc} are not expected to be significant.
Test Facility GS SA (2015)

Particle Size Inhalable fraction (< 100 μm): 37.85%
Respirable fraction (< 10 μm): 1.88%

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions

Range (μm)	*Mass (%)*
< 100	37.85
< 10	1.88
< 5	1.34

Remarks Determined using the laser diffraction method
Test Facility RCC (2008f)

Flash Point 160.3 °C at 100.2 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point
Remarks Determined using a Pensky-Martens flash point apparatus
Test Facility RCC (2008g)

Autoignition Temperature 400 °C

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

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (99.6% purity)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001)
Species/Strain	Rat/HanRcc:Wistar (SPF)
Vehicle	Polyethylene glycol 300
Remarks - Method	No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3F	2,000	0/3
2	3F	2,000	0/3

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No signs of toxicity were observed.
Effects in Organs	No abnormalities were observed during necroscopy.
Remarks - Results	No unscheduled mortalities occurred during the study. All animals showed expected body weight gain during the study.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	RCC (2005a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 402 Acute Dermal Toxicity (1987)
Species/Strain	Rat/HanRcc:Wistar (SPF)
Vehicle	Polyethylene glycol 300
Type of dressing	Semi-occlusive
Remarks - Method	No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5M/5F	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No unscheduled mortalities occurred during the study. Slight scaling (grade 1) was observed in all animals on day 6. Scaling persisted up to day 13 in all males and in 2 females, up to day 14 in 2 females and up to day 15 in 1 female. Slight scab (grade 1) was observed in 5 animals (2 males and 3 females) on day 6 and in 2 animals (1 male and 1 female) on day 7 and persisted up to day 9 in 1 female, up to day 10 in 2 females, up to day 11 in 1 male and up to day 13 in 2 males and in 1 female. Slight erythema (grade 1) was observed in 2 females on day 6 and persisted up to day 7 in one animal and day 9 in the other animal.
Signs of Toxicity - Systemic	No systemic toxicity was observed.
Effects in Organs	No abnormalities were observed during necroscopy.
Remarks - Results	Slight reduction (2.3%) in bodyweight gain was observed in a female animal during the first week but recovered until the end of the study. All

other treated animals showed expected body weight gain during the observation period.

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

TEST FACILITY RCC (2007a)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical (99.9% purity)

METHOD OECD TG 403 Acute Inhalation Toxicity (1981)
Species/Strain Rat/HanRcc:Wistar (SPF)
Vehicle Nil
Method of Exposure Nose only
Exposure Period 4 hours
Physical Form Solid aerosol (particulate)
Particle Size Mass median aerodynamic diameter (MMAD): 3.03 µm
Remarks - Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Concentration (g/m³)*		*Mortality*
		Nominal	*Actual*	
1	5M/5F	9.283	4.076	0/10

LC50 > 4.076 mg/L/4 hours
Signs of Toxicity No adverse clinical signs were observed.
Effects in Organs No abnormalities were observed at macroscopic examination.
Remarks - Results No unscheduled mortalities occurred during the study.

Actual concentration of the notified chemical obtained was less than 50% of the nominal concentration. The study authors stated that this was due to the accumulation of a significant proportion of the notified chemical in the exposure system.

CONCLUSION The notified chemical is of low acute toxicity via inhalation.

TEST FACILITY RCC (2007b)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical (99.9% purity)

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 3 (1M/2F)
Vehicle Moistened with water
Observation Period 72 hours
Type of Dressing Semi-occlusive
Remarks - Method No protocol deviations

RESULTS

Remarks - Results No signs of irritations were observed in any animal at any of the observation times.

No abnormal body weight changes were observed during the study.

CONCLUSION The notified chemical is not irritating to the skin.

TEST FACILITY RCC (2007c)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical (99.9% purity)

METHOD OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 1M/2F
Observation Period 7 days
Remarks - Method No protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	1	1	1	2	< 7 days	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	1	< 24 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

At the 1 hour observation, one male and one female showed slight (grade 1) reddening of the conjunctiva and one female showed moderate (grade 2) reddening of the conjunctiva. Slight reddening of the conjunctiva persisted in all animals at the 24 hour, 48 hour and 72 hour observations.

Slight ocular discharge was observed in all the animals at the 1 hour observation and no discharge was observed at the subsequent observations.

Slight (in one male and in one female) to moderate (in one female) reddening of the sclerae was observed in all animals at the 1 hour observation which persisted in one male at the 24 hour observation.

All signs of irritation were resolved at the 7-day observation.

No abnormal body weight changes were observed during the study. No unscheduled mortality or clinical signs of systemic toxicity was observed.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY RCC (2007d)

B.6. Skin sensitisation – mouse LLNA

TEST SUBSTANCE Notified chemical (99.6% purity)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/CaHsdRcc (SPF)
Vehicle Acetone:olive oil (4:1)
Preliminary study Not conducted
Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method No significant protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4F	278	-
10	4F	879	3.2
25	4F	1604	5.8
50	4F	2453	8.8
Positive Control			
0 (vehicle control)	4F	314	-
5	4F	910	2.9
10	4F	1223	3.9
25	4F	2725	8.7

EC3 9.3%

Remarks - Results No unscheduled mortalities or signs of systemic toxicity were observed during the study period.

The stimulation indices were 3.2, 5.8 and 8.8 at 10%, 25% and 50% concentrations, respectively, indicating a sensitising response. The stimulation index (EC3) was calculated to be 9.3%.

All animals exposed to 50% of the notified chemical showed residue of the notified chemical in the treated ears.

The positive control behaved as expected, confirming the validity of the test system.

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

TEST FACILITY RCC (2005b)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical

METHOD Repeated insult patch test with challenge

Study Design Induction Procedure: Patches containing 0.2 mL (2.5%) of the test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications during the induction period. Patches were removed by the subjects after 24 hours and graded by technicians after an additional 24 hours (or 48 hours for patches applied on Friday).
Rest Period: ~ 14 days
Challenge Procedure: Patches were applied to a naive site. The sites were scored 24, 48 and 72 hours after application.

Study Group 86 F/19 M; age range 18 to 79 years.

Vehicle Ethanol:diethyl phthalate (1:3)

Remarks - Method The test substance was applied on a 2 cm^2 occlusive patch.

RESULTS

Remarks - Results 101/105 subjects completed the study. Four subjects discontinued with the study for reasons unrelated to the test substance.

No adverse responses were observed at induction and challenge.

CONCLUSION The notified chemical at 25% concentration was non-sensitising under the conditions of the test.

TEST FACILITY ETC (2010)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (1996)
Species/Strain	Rat/HanRcc:Wistar (SPF)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Polyethylene glycol 300
Remarks - Method	No recovery groups were included in the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
control	5M/5F	-	0/10
low dose	5M/5F	50	0/10
mid dose	5M/5F	200	0/10
high dose	5M/5F	1,000	0/10

Mortality and Time to Death

No unscheduled mortalities occurred during the study.

Clinical Observations

No treatment related changes in body weight, body weight gain, and food and water consumption were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No treatment related changes were noted in the haematology parameters.

Statistically significant treatment-related changes in biochemistry parameters consisted of:

- reduced glucose level in males treated at 1,000 mg/kg bw/day (21.6% reduction compared to control group)
- increased alanine amino transferase in females treated at 1,000 mg/kg bw/day (33% increase compared to control group). The study authors regarded this effect to be an adaptive change and considered to be non-adverse.
- increased urea in females treated at 1,000 mg/kg bw/day (17.8% increase compared to control group)
- increased sodium (1.5% increase compared to control group) and globulin (16% increase compared to control group) and reduced potassium (18% reduction compared to control group) and chloride (5% reduction compared to control group) in females treated at 1,000 mg/kg bw/day. Reduced albumin:globulin ratio was also observed in females treated at 1,000 mg/kg bw/day (18.7% reduction compared to control group).

Effects in Organs

Organ weights

Treatment related differences in absolute and/or relative organ weights were noted in the liver, kidney and adrenals.

- Increased absolute and relative liver weights were observed in females treated at 200 mg/kg bw/day (27.5% and 26.5% increase compared to control groups in absolute and relative liver weights, respectively) and at 1,000 mg/kg bw/day (27.6% and 30.8% increase compared to control groups in absolute and relative liver weights, respectively). In males, increased absolute and relative liver weights were observed at 200 mg/kg bw/day (28.4% and 18.2% increase compared to control groups in absolute and relative liver weights, respectively) and at 1,000 mg/kg bw/day (14.3% and 18.4% increase compared to control groups in absolute and relative liver weights, respectively). The liver:brain weight was increased at 200 mg/kg bw/day in males (20.7% increase compared to control group) and at 200 mg/kg bw/day (27.5% increase compared to control group) and at 1,000 mg/kg bw/day (27.9% increase compared to control group) in females.
- Increased absolute kidney weights were observed in females treated at 200 mg/kg bw/day (14%

increase compared to control group) and at 1,000 mg/kg bw/day (17% increase compared to control group). Increased relative kidney weights were observed in males and females treated at 1,000 mg/kg bw/day (14.5% increase compared to control group in males and 19.5% increase compared to control group in females).

- Increased relative heart weight was observed in females treated at 1,000 mg/kg bw/day (17.5% increase compared to control group).
- In addition, increased absolute adrenal weight were observed inmales treated at 50 mg/kg bw/day (29.5% increase compared to control group) and females treated at 1,000 mg/kg bw/day (20% increase compared to control group; not significant). Increased relative adrenal weight was observed for both sexes treated at 1,000 mg/kg bw/day (33.3% and 24% increase compared to control groups in males and females, respectively). In the absence of morphological evidence, the higher adrenalin gland weight is considered to be non-adverse by the study authors.

Macroscopic findings
No treatment related macroscopic findings were noted.

Microscopic findings

- In the liver, minimal hepatocellular hypertrophy was observed in animals treated at 200 mg/kg bw/day and minimal to slight hepatocellular hypertrophy was observed in animals treated at 1,000 mg/kg bw/day.
- In the kidneys, increased incidences of minimal tubular basophilia were observed in both sexes at all doses (in four males at all concentrations and five females at 50 mg/kg bw/day, five females at 200 mg/kg bw/day and three females at 1,000 mg/kg bw/day), but without any clear evidence of degenerative change.
- In the heart, minimal to marked myocardial vacuolation was observed in animals treated at 200 mg/kg bw/day and 1,000 mg/kg bw/day. The oil red stain of the hearts of animals treated at 1,000 mg/kg bw/day was negative, therefore no evidence for fatty vacuolation of the myocardial cells. The study authors stated that as there were no recovery groups, a prognosis of this lesion could not be established and hence was considered to be of adverse degenerative character.
- In adrenal glands, one female treated at 200 mg/kg bw/day and two females treated at 1,000 mg/kg bw/day showed minimal hypertrophy of the zona fasciculate. The study authors indicated that given the slight nature of hypertrophy of the zona glomerulosa of the adrenal glands, and absence of any degenerative findings, this effect was considered to be non-adverse.
- In the epididymides, a moderate sperm granuloma (unilateral) was observed in two males treated at 1,000 mg/kg bw/day. The study authors indicated the reason for this change was unclear.

Remarks – Results
Treatment related effects were observed in the liver, kidneys, heart and adrenal glands; however, the effects in the liver and adrenal glands were considered non-adverse by the study authors. Furthermore, the increase in minimal tubular basophilia in the kidneys of animals at all doses was observed without any clear evidence of degenerative change. Myocardial vacuolation in the heart of animals treated at 200 mg/kg bw/day and 1,000 mg/kg bw/day was considered to be of adverse degenerative nature by the study authors in the absence of a recovery group.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 50 mg/kg bw/day in this study based on myocardial vacuolation in the heart of animals treated at 200 mg/kg bw/day and 1,000 mg/kg bw/day.

TEST FACILITY RCC (2008i)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (99.6% purity)

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997)
Species/Strain *Salmonella typhimurium*: TA1535, TA1537, TA98 and TA100
Escherichia coli: WP2uvrA
Test 1 – plate incorporation method; Test 2 – preincubation method

Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	Preliminary test/Test 1: With or without metabolic activation: 3, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate Test 2: With or without metabolic activation: 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate
Vehicle	Dimethylsulfoxide (DMSO)
Remarks - Method	A preliminary test at a concentration range of 3.0 – 5,000 µg/plate (with and without metabolic activation) was conducted on TA98, TA100, TA1535, TA1537 and WP2uvrA. As no toxicity was observed up to 5,000 µg/plate, the preliminary study is reported as Test 1. Vehicle and positive control studies were conducted in parallel with the main study. Negative control: DMSO Positive control: With metabolic activation: 2-aminoanthracene (TA98, TA100, TA1535, TA1537 and WP2uvrA) Without metabolic activation: sodium azide (TA1535 and TA100), 4-nitro-o-phenylene-diamine (TA98 and TA1537) and methyl methane sulfonate (WP2uvrA). No significant protocol deviations.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5,000	> 5,000	≥ 5,000	Negative
Test 2		> 5,000	≥ 5,000	Negative
Present				
Test 1	> 5,000	> 5,000	≥ 2,500	Negative
Test 2		> 5,000	≥ 5,000	Negative

Remarks - Results	No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with the test substance at any dose level, in the presence or absence of metabolic activation. There were also no dose dependent increases in mutation rates. In Test 2, with metabolic activation, the number of revertant colonies in the negative and solvent control strain of WP2uvrA exceeded the historical control range. The authors stated that this has no toxicological significance. The positive controls gave satisfactory responses, confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	RCC (2005c)

B.10. Genotoxicity – *in vitro* Chines hamster V79 cells

TEST SUBSTANCE	Notified chemical (99.9% purity)

METHOD: OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (1998)

Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Acetone
Remarks - Method	Negative control: acetone Positive control: without metabolic activation - ethylmethane sulfonate with metabolic activation - cyclophosphamide In a range finding study, V79 cells were treated with the notified chemical at 16.4 to 2,100 µg/mL for 4 hours with or without metabolic activation, and for 24 hours without metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	3.1*, 6.3*, 12.5*, 25.0, 50.0 and 100.0	4 h	18 h
Test 2	3.1, 6.3*, 12.5*, 25.0*, 50.0 and 100.0	18 h	18 h
Test 2a	12.5, 25.0*, 50.0* and 100	28 h	28 h
Present			
Test 1	3.1, 6.3, 12.5*, 25.0*, 50.0* and 100.0	4 h	18 h
Test 2	3.1, 6.3, 12.5*, 25.0*, 50.0* and 100.0	4 h	28 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test (> 50%)	*Cytotoxicity in Main Test (> 50%)*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 65.6	> 100.0	≥ 100.0	Negative
Test 2	≥ 32.8	≥ 25.0	> 100.0	Negative
Test 2a		≥ 50.0	> 100.0	Negative
Present				
Test 1	≥ 65.6	> 100.0	≥ 25.0	Negative
Test 2		≥ 50.0	> 100.0	Negative

Remarks - Results

In Test 1 with metabolic activation at 25 µg/mL a statistically significant increase in the number of aberrant cells, excluding gaps was observed. However, the percentage of aberrant cells (4%), excluding gaps at this concentration was lower than the historical control range of the test facility. This finding was considered by the study authors to be biologically irrelevant as it was within the testing facility's historical control data range.

In both tests, no biologically relevant increase in structural chromosomal aberrations was observed with or without metabolic activation.

The positive controls behaved as expected, confirming the validity of the test system.

CONCLUSION: The notified chemical was not clastogenic to V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY: RCC (2008j)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge (origin not reported)
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Oxygen consumption using an electrode-type manometer
Remarks - Method	No significant deviation from the test guidelines was reported. Sodium benzoate was used as a reference item (procedural control; 100mg/L). An inoculum blank and a toxicity control (30 mg/L GR-86-6414, and 100 mg/L sodium benzoate) were also included in the test design. The test item treatment (in duplicate) was 30 mg/L, corrected for uptake by the blank inoculum.

RESULTS

Day	*Test substance* % Degradation		*Day*	*Sodium benzoate* % Degradation	
	Replicate 1	Replicate 2		Replicate 1	Replicate 2
2	0	0	2	47	47
10	1(1)	0(0)	10	86	88
14	1 (1)*	-1 (-1)*	14	89	91
28	0 (0)*	1 (1)*	28	91	93

* $ThOD_{NO3}$ ($ThOD_{NH4}$)

Remarks - Results	All validity criteria were met. Biodegradation in the toxicity control was > 25% within 14 days. Therefore, no inhibitory effects were observed for the test item. The percent biodegradation of the test item was calculated based on the theoretical oxygen demand without nitrification ($ThOD_{NH4}$) and with nitrification ($ThOD_{N03}$). No information on abiotic degradation was reported.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	RCC (2008k)

C.1.2. Photodegradation

TEST SUBSTANCE	Notified chemical (99% purity)
METHOD	OECD TG 316 Photo-transformation of Chemicals in Water - Direct Photolysis EC Directive 91/414/EEC, Annex II; Paragraph 7.2.1.3. Photochemical Degradation, 7.2.1.2
Light source and Spectrum	Suntest XLS (Atlas Material Testing Solutions, Germany), which is fitted with a Xenon arc lamp and simulates the sunlight spectrum in summer at latitudes 30 to 50°N.
Relative Intensity	Mean intensity of the artificial light penetrating the surfaces of the aqueous solutions in the range of 300 to 400 nm was about 46 and 45 W/m^2, respectively.
Spectrum of Test Substance	Maximum absorbance 200 to 300 nm
Exposure Period	7 days of natural sunlight (12 days of mid-summer at latitudes 40 and 13 days at 50 °N).
Remarks – Method	There were no major deviations from the TG reported. The test design was

laboratory-based with simulated sunlight.

RESULTS

Remarks - Results	Recoveries of the test items from analysis were not reported, but variation in duplicate analysis is low. Levels of the test substance in the dark controls reduced significantly over time. This was attributed to volatility of the test substance, despite efforts to control such factors. The LOD was 0.010 µg/mL for analysed water samples. The half-life of the notified chemical was not able to be determined.
CONCLUSION	The results indicate that the notified chemical is resistant to photolysis in surface waters. The losses from photolysis could not be differentiated from the large losses due to volatilisation.
TEST FACILITY	IES (2010)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish
Species	*Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	125 mg $CaCO_3$/L
Analytical Monitoring	HPLC coupled with a Ultraviolet–visible detector (HPLC-UV/VIS)
Remarks – Method	
RESULTS	A limit test was conducted based on the results of a range finding test, where fish were exposed to the test item at a nominal concentration of 100 mg/L (mean measured = 1.3 mg/L). A control was also included in the limit test design. The test involved daily renewal of the test medium. Temperature (22 to 23 °C) and dissolved oxygen levels [≥ 8 mg O_2/L (> 60% of the air saturation value)] were kept relatively stable throughout the test. No significant deviations from the test guidelines were reported.

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	< LOD	7	0	0	0	0	0
100	1.3	7	0	0	0	0	0

LC50	> 1.3 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The test preparations were observed to be clear solutions for all test media throughout the test. There were no sub-lethal effects of exposure observed in seven fish exposed to the test substance.
CONCLUSION	The notified chemical is not toxic to fish to the limits of its water solubility.
TEST FACILITY	RCC (2008l)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction

	Test - static EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV/VIS
Remarks - Method	No significant deviations from the test guidelines were reported. A limit test was conducted at a concentration above the water solubility limit of the test chemical, where daphnid were exposed to a nominal concentration of the test item of 100 mg/L. A control was also included in the limit test design. An acute immobilization using a reference item (potassium dichromate) is run twice a year at the testing facility.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	0	20	0	0
100	0.82	20	0	0

LC50	> 0.82 mg/L at 48 hours
Remarks - Results	The test was considered valid. At the beginning and end of the test period, the dissolved oxygen concentration in the test medium and control was > 8 mg/L. The 48-hour EC50 for the reference compound was 0.53 mg/L, indicating that the sensitivity of the test organisms was within the historical range of the test facility (0.53-1.1 mg/L). There was no immobilisation or other toxic effects in the test group relative or the control at the limit dose tested, which is at the water solubility limit.

CONCLUSION The notified chemical is not toxic to aquatic invertebrates to the limits of its water solubility.

TEST FACILITY RCC (2008m)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical (99.95 purity)

METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Council Regulation No 440/2008 C.3 Algal Inhibition Test
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: undiluted filtrate (100 mg/L) Actual: 1.3 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV/VIS
Remarks - Method	No significant deviations from the test guidelines were reported.

RESULTS

Yield *EyC50* *mg/L at 72 h*	*Growth* *ErC50* *mg/L at 72 h*
> 1.3	> 1.3

Remarks - Results	In the control the biomass increased by a factor of 123 over 72 hours. The mean coefficient of variation of the daily growth rates in the control (section-by-section growth rates) during 72 hours was 16%. The

	coefficient of variation of the average specific growth rates in the replicates of the control after 72 hours was 0.8%. Therefore, all validity criteria for the test were satisfied. All test media remained clear throughout the test period, and there were no significant observations made regarding the appearance of the test media. There were no significant inhibitory effects on the algal growth at the tested concentrations.
CONCLUSION	The notified chemical is not toxic to algae to the limits of its water solubility.
TEST FACILITY	RCC (2008n)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Aerobic activated sludge from a wastewater treatment plant treating predominantly domestic wastewater.
Exposure Period	3 hours
Concentration Range	Nominal: 1,000 mg/L Actual: not measured
Remarks – Method	There were no major deviations from the test guidelines. The test was carried out based on results of a range-finding test. The test item was not measured over the duration of the test. 3,5-dichlorophenol was used as the reference item (5, 16 and 50 mg/L).
RESULTS	
IC50	1,000 mg/L
Remarks – Results	All validity criteria for the test were satisfied. The 3-hour EC50 (14 mg/L) of the reference item 3,5-dichlorophenol was calculated by Probit analysis.
CONCLUSION	Not inhibitory to microbial respiration.
TEST FACILITY	RCC (2008o)

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