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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexadecen-1-one

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/2007	Symrise Pty Ltd	Cyclohexadecen-1-one	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 corrosion/irritation (Category 2)	H315 - Causes skin irritation

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 toxic effects up to the limit of 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 irritation (Category 2): H315 - Causes skin irritation

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

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 to the notified chemical during reformulation processes:

- Avoid skin and eye contact

- 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

  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 notified 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.

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 intended to exceed 6.5% in cosmetic and household products;
  - further information becomes available on the skin sensitisation potential of the notified chemical;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
  - the amount of chemical being introduced has increased, or is likely to increase, significantly;

- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

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
Symrise Pty Ltd (ABN: 67 000 880 946)
168 South Creek Road
DEE WHY NSW 2099

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
None

NOTIFICATION IN OTHER COUNTRIES
EU (2011), Philippines (2016)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Aurelione

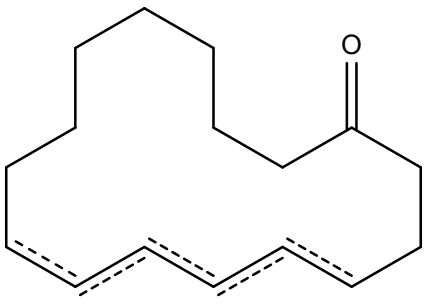
CAS NUMBER
88642-03-9

CHEMICAL NAME
Cyclohexadecen-1-one

OTHER NAMES
Cyclohexadecenone
Reaction mass of trans-cyclohexadecen-8-one, cis-cyclohexadecen-8-one, trans-cyclohexadecen-7-one, cis-cyclohexadecen-7-one

MOLECULAR FORMULA
$C_{16}H_{28}O$

STRUCTURAL FORMULA
The notified chemical is a mixture of isomers (see Section 3 for composition details).



The double bond may be in the 4, 5, 6, 7 or 8 position and may be E or Z configuration.

MOLECULAR WEIGHT
236.44 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
98.7% (sum of all isomers)

The notified chemical is manufactured as an isomer mixture.

The typical composition of the notified chemical in the isomer mixture (Aurelione) is as follows:

Notified chemical	Weight %
(8E)-Cyclohexadec-8-en-1-one and cyclohexadec-6-en-1-one isomer I	41.08
(7E)-Cyclohexadec-7-en-1-one	28.58
(8Z)-Cyclohexadec-8-en-1-one and cyclohexadec-6-en-1-one isomer II	12.47
(7Z)-Cyclohexadec-7-en-1-one	7.42
Cyclohexadec-4-en-1-one isomer I	4.18
Cyclohexadec-4-en-1-one isomer II	2.05
Cyclohexadec-5-en-1-one isomer I and cyclohexadec-5-en-1-one isomer II	2.89

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: Colourless to pale yellow liquid to crystals

Property	Value	Data Source/Justification
Melting Point/Freezing Point	25 °C	Measured
Boiling Point	352 °C at 101.3 kPa	Measured
Density	940.7 kg/m^3 at 22.5 °C	Measured
Vapour Pressure	2.1×10^{-5} kPa at 25 °C	Measured
Water Solubility	0.982 mg/L at 20 °C	Measured. The notified chemical is slightly soluble in water and increases with pH, but not with temperature
Hydrolysis as a Function of pH	Hydrolytic degradation was 24%, 30% and 9% after 120 hours at 50 °C at pH of 4, 7 and 9, respectively	Measured. The notified chemical is susceptible to hydrolysis under environmental conditions (pH 4-9) Hydrolysis is more rapid in neutral and acidic conditions.
Partition Coefficient (n-octanol/water)	log Pow = 6.5 at 23 °C	Measured. The log Pow represents the weighted average mean of the 10 isomers
Adsorption/Desorption	log K_{oc} (soil) = 4.23 at 22 °C	Measured. Weighted average mean based

Property	Value	Data Source/Justification
	log K_{oc} (sludge) = 4.49 at 22 °C	on the peak area of the 5 respective (isomer) signals was calculated
Dissociation Constant	Not determined	The molecule does not contain ionisable functionalities, and hence is not expected to dissociate under normal environmental conditions (pH 4-9)
Flash Point	170 °C	SDS
Flammability	Not highly flammable	Measured
Autoignition Temperature	250 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for 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. It will be imported into Australia as a component of finished consumer products such as fine fragrances, other cosmetic products and household cleaning products, at ≤ 6.5% concentration. The notified chemical may also be imported into Australia as a component of fragrance mixtures at ≤ 45% concentration, a solution of the notified chemical at ≤ 12% concentration or in its neat form.

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

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

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
Symrise Pty Ltd (the notifier)

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of finished products at a concentration of ≤ 6.5% packed in containers suitable for retail sale; in neat form or as a solution at < 12% concentration in 30 L steel cans; or as a component of a fragrance mixtures at < 45% concentration in 30 L and 216 L metal drums and 30 L HDPE/EVOH plastic canisters.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products at ≤ 6.5% concentration.

Concentration of the notified chemical in finished consumer products will be as follows:

Finished Consumer Product	*Final Concentration of the Notified Chemical (%)*
Fine fragrance	0.2 – 6.5
Other cosmetic products	0.02 – 0.8
Household cleaning products	0.01 – 0.3

OPERATION DESCRIPTION

Reformulation of the notified chemical or fragrance mixtures containing the notified chemical at ≤ 45% concentration into finished consumer goods may vary depending of the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end-use products into containers of various sizes.

End-use products containing the notified chemical (at ≤ 6.5% concentration) will be used by consumers and professionals such as hairdressers, beauticians and cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	1	2
Mixing	4	2
Drum handlers	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	0.5	2
Packaging	4	2
End users (professionals)	1- 8	200

EXPOSURE DETAILS

Transport and distribution

Transport, storage and warehouse workers may come into contact with the notified chemical in its neat form, at ≤ 45% concentration in fragrance mixtures, at ≤ 12% concentration in solutions or at ≤ 6.5% 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 in its neat form or at ≤ 45% 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 suitable gloves.

End-use

Exposure to the notified chemical in end-use products (at ≤ 6.5% 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 ≤ 6.5% concentration through the use of a wide range of cosmetic and household products containing the notified chemical. 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 provided in various literatures (SCCS, 2010; 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 used 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% of the exposed concentration. 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	0.8	1	0.9775
Face cream	1540	0.8	1	0.1925
Hand cream	2160	0.8	1	0.2700
Fine fragrances	750	6.5	1	0.7617
Deodorant spray	1430	0.8	1	0.1875
Shampoo	10460	0.8	0.01	0.0131
Conditioner	3920	0.8	0.01	0.0049
Shower gel	18670	0.8	0.01	0.0233
Hand soap	20000	0.8	0.01	0.0250
Hair styling products	4000	0.8	0.1	0.0500
Total				**2.5055**

C = maximum intended concentration of notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household products (Indirect dermal exposure from clothes):

Product type	**Amount** (g/use)	**C** (%)	**Product Retained (PR)** (%)	**Percent Transfer (PT)** (%)	**Daily systemic exposure** (mg/kg bw/day)
Laundry liquid	230	0.3	0.95	10	0.0102
Fabric softener	90	0.3	0.95	10	0.0040
Total					**0.0143**

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	0.3	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.3	1980	0.0093	0.01	0.03	0.0008
All-purpose cleaner	1	0.3	1980	1	0.01	0.007	0.0065
Total							**0.0073**

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	C	Inhalation rate	Exposure duration zone 1	Exposure duration zone 2	Fraction inhaled	Volume zone 1	Volume zone 2	Daily systemic exposure
	(g/use)	(%)	(m^3/day)	(min)	(min)	(%)	(m^3)	(m^3)	(mg/kg bw/day)
Hairspray	20	0.8	20	15	20	50	1	10	**0.0258**

C = maximum intended concentration of notified chemical

Total daily systemic exposure from inhalation was calculated by using the daily systemic exposure from Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] and daily systemic exposure from 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 2.5529 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 (with a 100% absorption rate), is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetics and household products with lower exposure factors.

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
Rabbit, skin irritation (1)	mildly irritating
Rabbit, skin irritation (2)	irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Mouse, skin sensitisation – modified Local lymph node assay (LLNA) (non-OECD guideline study)	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL > 1,000 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 (236.44 g/mol) the notified chemical may be absorbed across the respiratory or gastrointestinal tract. However, based on the low water solubility (0.982 mg/L at 20 °C) and high partition coefficient (log Pow = 6.5 at 23 °C), indicating a reasonably high lipophilicity, percutaneous absorption would be limited.

Acute toxicity

The notified chemical was found to be of low acute oral and dermal toxicity in rats.

No studies were submitted for acute inhalation toxicity of the notified chemical.

Irritation and sensitisation

Two skin irritation studies conducted in rabbits with two different vehicles were submitted for the notified chemical.

In the first study (with ethanol/diethyl phthalate (1:1) as the vehicle), all animals showed well defined erythema and two animals showed very slight to slight oedema. No erythema or oedema was observed at the 7 day observation. Scales were observed in one animal at the day 7 and day 14 observations. All signs of irritation

were fully resolved at the day 21 observation. Based on the results of this study, the notified chemical is mildly irritating to the skin.

In the second study (with olive oil as the vehicle), moderate to severe erythema and oedema was observed with two animals displaying eschar formation. No erythema or oedema was observed at the day 7 observation. Scales were observed at the day 7 and day 14 observations. At the day 21 observation all animals were free of any signs of irritation. Based on the results of this study, the notified chemical is irritating to the skin, warranting hazard classification according to the GHS criteria.

In a study conducted in rabbits, the notified chemical was found to be slightly irritating to eyes. Slight to moderate conjunctival irritation and corneal opacity and slight iridial inflammation were observed in all animals. Only 1 out of 3 rabbits showed corneal opacity meeting the hazard classification criteria under the GHS. All signs of irritation were resolved at the 6-day observation.

Sensitisation
Two skin sensitisation studies were submitted for the notified chemical.

In a guinea pig maximisation test (OECD TG 406), the notified chemical was not a skin sensitiser. However in a modified local lymph node assay (LLNA) non-OECD guideline study the notified chemical gave a positive response.

The modified LLNA used a non-radioactive method and was based on lymph node cell count (LNCC). The method also incorporated the Integrated Model for the Differentiation of Skin reactions (IMDS) (Homey et al., 1998). The IMDS serves to distinguish between an inflammatory (non-specific) and an allergic (specific) reaction. A differentiation index (DI) > 1 is considered an allergic reaction whereas a DI < 1 is considered an inflammatory response. In the study the LNCC increased at all test concentrations resulting in stimulation indices (SI) of 1.29, 1.33 and 1.50 for test concentrations of 10%, 25% and 50%, respectively. In the study report a SI of 1.25 was considered as a positive threshold for the strain of mice used. The corresponding differentiation indices (DI) were 3.88, 3.98 and 4.49 exceeding the threshold of 1.00 for an allergic reaction. The study authors therefore concluded that the notified chemical was a skin sensitiser. However, in the study a significant ear weight increase at all test concentrations is noted which was not discussed in the study, but might be interpreted as a sign of non-immune tissue stimulation. In addition, it has been reported that the LLNA tends to produce false positive results with skin irritants (OECD TG 429, 2010) and aliphatic compounds containing isolated unsaturated carbon-carbon bonds, similar to the notified chemical (Kreiling et al., 2008).

Given the uncertainties with the modified LLNA, the lack of a structural alert for skin sensitisation and negative result in a well-conducted GPMT study, the notified chemical is not considered to be a skin sensitiser.

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 100, 300, and 1,000 mg/kg bw/day. Statistically significant and treatment related increases in absolute and relative liver weights in males (at all doses) and females (at 1,000 mg/kg bw/day) were observed and there was evidence of a dose response in both sexes. These findings, however, were not accompanied by associated clinical pathology or histopathological findings and were considered an adaptive response to a xenobiotic. The study authors established a No Observed Adverse Effect Level (NOAEL) for systemic toxicity as greater than 1,000 mg/kg bw/day based on the absence of toxicologically significant effects at any dose tested.

Mutagenicity/Genotoxicity
The notified chemical was negative in a bacterial reverse mutation assay and in an *in vitro* chromosomal aberration test in human lymphocytes.

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 corrosion/irritation (Category 2)	H315 - Causes skin irritation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the toxicological information provided, the notified chemical is a skin irritant and slightly irritating to eyes.

Reformulation

During reformulation workers may be at risk of irritation effects when handling the notified chemical in its neat form and at ≤ 45% concentration. It is anticipated that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection) will be used to limit worker exposure. Therefore, 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 and household products containing the notified chemical to clients (*e.g.*, hairdressers, beauty salon workers and cleaners) or the use of household products in the cleaning industry may be exposed to the notified chemical at ≤ 6.5% 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.

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

6.3.2. Public Health

Based on the toxicological information provided, the notified chemical is a skin irritant and slightly irritating to eyes. At the proposed low use concentration (≤ 6.5%) in cosmetic and household products, significant irritation effects are not expected.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 6.5% concentration in cosmetic and household products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia in its neat form, as a component of fragrance mixtures or in solution for reformulation into finished cosmetic and household cleaning products, or as a component of finished cosmetic and household cleaning products. There is unlikely to be any significant release of the notified chemical to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the products containing the notified chemical is expected to be collected with absorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment followed by automated filling of the reformulated end-use products into containers of various sizes. Wastes containing the notified chemical generated during reformulation include equipment wash water (estimated to be < 1% of the import volume by the notifier), residues in empty import containers and spilt materials. Wash waters are expected to be released to on-site waste water treatment processes, or sewers in a worst case scenario. Empty import containers and residues 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 compartment through sewers during its use in cosmetic and household cleaning products across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL

Only a small amount of residue is expected to remain in containers upon disposal. Wastes and residues of the notified chemical in empty end-use 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. The submitted biodegradation studies indicate that the notified chemical is expected to be rapidly degraded in sewage treatment plants (STPs). For the details of the environmental fate studies refer to Appendix C.

Fate in air is not considered important for exposure because the notified chemical is only slightly volatile (vapour pressure = 2.1×10^{-5} kPa at 25 °C), and hence is expected to be present in air at low levels. Any notified chemical released to the atmospheric compartment is not expected to persist. The half-life of the notified chemical in air is calculated to be 1.6 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA 2012).

In STPs a significant proportion of the notified chemical is expected to be associated with the sewage sludge phase, based on its low water solubility and lipophilicity (log Pow = 6.5). Therefore, a significant proportion of the notified chemical may be removed during sewage treatment, thus reducing its release to surface waters. A proportion of the notified 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 notified chemical is not expected to be mobile in soil and sludge (McCall et al., 1980) based on its organic carbon-water partition coefficient values in these matrices [log Koc (soil) = 4.2 and log Koc (sludge) = 4.5].

The notified chemical has the potential to bioaccumulate based on its octanol-water partition coefficient value (log Pow = 6.5). For purposes of determining bioaccumulative potential and in the absence of any measured BCF or BAF, a log Pow > 4.2 indicates that the notified chemical has the potential to bioaccumulate (EPHC, 2007). The notified chemical is expected to degrade via biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated 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 log Pow of the notified chemical, as well as its ready biodegradability, it was assumed there will be 93% removal of the notified chemical during sewage treatment processes. 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:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.4	million
Removal within STP	93%	
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10	
PEC - River:	0.039	µg/L
PEC - Ocean:	0.0039	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 1,500 kg/m^3). As explained above it is expected that most of the notified chemical will be removed during the sewage treatment process. Using these assumptions, irrigation with a concentration of 0.039 µg/L may potentially result in a soil concentration of approximately 0.26 µg/kg.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 4.045 mg/kg (dry weight). 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 be approximately 0.027 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application.

The notified chemical is readily biodegradable, and hence is not expected to accumulate in soil after irrigation with sewage effluent or biosolid application.

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 > 0.35 mg/L 96 h LC50 > 0.29 mg/L	Not toxic to fish up to water solubility limit
Daphnia Toxicity	48 h EC50 > 0.85 mg/L	Not toxic to aquatic invertebrates up to water solubility limit
Algal Toxicity	72 h ErC50 > 0.91 mg/L	Not toxic to algae up to water solubility limit
Inhibition of Bacterial Respiration	IC50 > 1,000 mg/L	Not inhibitory to microbial respiration

The notified chemical is determined to be not toxic to aquatic life up to the water solubility limit on acute basis. Therefore, the notified chemical cannot be classified according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009).

Taking into account that the notified chemical is likely to rapidly biodegrade it has not formally classified as a long-term aquatic hazard.

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

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. The notified chemical has bioaccumulation potential based on its log Kow. However, the notified chemical is expected to biodegrade rapidly, and will partition to sludge and soil. Thus the notified chemical is unlikely to persist in the environment or be bioavailable. Therefore, based on the assessed use pattern in cosmetic and household products, the fate of the notified chemical in the STP, and on no observed toxic effects to the limits 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 25 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined using differential scanning calorimetry.
Test Facility	Siemens AG (2004a)

Boiling Point 352 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Determined using differential scanning calorimetry
Test Facility	Siemens AG (2004a)

Density 940.7 kg/m^3 at 22.5 °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	Siemens AG (2007a)

Vapour Pressure 2.1×10^{-5} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Effusion method
Test Facility	Siemens AG (2004b)

Water Solubility 0.98 mg/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Column Elution Method
Test Facility	GAB (2005a)

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

pH	*T (°C)*	*Hydrolysis time (hours)*	*% Degradation*
4	50	120	24
7	50	120	30
9	50	120	9

Remarks	Validity criteria of the test guideline were met. But, only a preliminary test was performed, and half-lives were not determined.
Test Facility	UN-Lab (2007)

Partition Coefficient (n-octanol/water) log Pow = 6.5 at 23 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method. The weighted average mean log Pow was based on the peak area of the signals from seven respective isomers of the notified chemical.
Test Facility	NL GmbH (2017a)

Adsorption/Desorption – main test log K_{oc} = 4.23 at 22 °C (soil) and log K_{oc} = 4.49 at 22 °C (sludge)

Method	OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
Remarks	The weighted average mean log Pow for soil and sludge was based on the peak areas of five isomer signals. The Koc in soil and sludge for the 5 isomers evaluated ranged from 4.13 to 4.37 and 4.37 to 4.67, respectively.
Test Facility	NL GmbH (2017b)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids)
Remarks	A temperature of > 1,000 °C was used in the study.
Test Facility	Bayer (2003)

Autoignition Temperature 250 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Conducted in an auto-ignition temperature apparatus
Test Facility	Siements AG (2007b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (93.9% purity)
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure
Species/Strain	Rat/Wistar SPF
Vehicle	Olive oil
Remarks - Method	A sighting study was conducted in a female rat at a dose of 2,000 mg/kg bw. Piloerection was observed 30 minute after dosing. Two hours after dosing, a hunched posture and piloerection were observed. No signs of toxicity were noted from day 1 until the end of the study period (14 days). No abnormalities were observed at necropsy. Based on the results of the screening study, the dose selected for the main study was 2,000 mg/kg bw. No protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Piloerection and hunched posture were observed in all animals 30 minutes after dosing which persisted up to day 1 of the observation. Tremor was observed in one animal 4 hours after dosing and in all animals at 6 hours. All animals appeared normal from day 2 until the end of the study period (14 days).
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	No unscheduled mortalities occurred during the study. All animals showed expected gains in bodyweight over the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	FREY-TOX (2003a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (88.5% purity)
METHOD	OECD TG 402 Acute Dermal Toxicity
Species/Strain	Rat/CD/Crl
Vehicle	Sesame oil
Type of dressing	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 signs of local toxicity were observed.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed.
Effects in Organs	No abnormalities were observed at necropsy.

Remarks - Results	The animals showed expected body weight gain over the observation period.
CONCLUSION	The notified chemical is of low acute toxicity via the dermal route.
TEST FACILITY	LPT (2007a)

B.3. Irritation – skin

Test Substance	Notified chemical (98.5% purity)
Method	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/Albino SPF
Number of Animals	3 F
Vehicle	Ethanol and diethyl phthalate (1:1)
Observation Period	21 days
Type of Dressing	Semi-occlusive
Remarks - Method	No protocol deviations.

Results

Lesion	*Mean Score**			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2.00	1.33	2.00	2.00	< 7 days	0.0
Oedema	1.67	0.00	0.67	2.00	< 7 days	0.0

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

Remarks - Results	All animals showed well defined erythema at the 1 hour observation which persisted in two animals up to the 72-hour observation. The remaining animal showed well defined erythema at the 24- and 48-hour observation and very slight erythema at the 72-hour observation. Very slight to slight oedema was observed in two animals up to the 48-hour observation. Very slight oedema persisted in one animal at the 72-hour observation. In one animal, no oedema was observed. No erythema or oedema was observed at the 7 day observation. Scales were observed in one animal at the day 7 and day 14 observations. No scales were observed at the day 21 observation.
Conclusion	The notified chemical is slightly irritating to the skin.
Test Facility	FREY-TOX (2004a)

B.4. Irritation – skin

TEST SUBSTANCE	Notified chemical (93.9% purity)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/Albino SPF
Number of Animals	3 F
Vehicle	Olive oil
Observation Period	21 days
Type of Dressing	Semi-occlusive
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			
Erythema/Eschar	3.00	3.67	4.00	4	< 7 days	0.0
Oedema	2.00	3.00	3.33	3	< 7 days	0.0

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

Remarks - Results

Moderate to severe erythema was observed in all animals up to the 72-observation with two animals displaying eschar formation from the 24- or 48-hour observation.

Moderate to severe oedema was observed in two animals up to the 72-hour observation period. Slight oedema was noted in the remaining animal.

No erythema or oedema was observed at the day 7 observation.

At the day 7 observation, two animals showed flat, yellow scales and the remaining animal showed slight crusty scales.

At the day 14 observation isolated scales were still noted in all animals.

At the day 21 observation all animals were free of any signs of irritation.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY FREY-TOX (2003b)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical (95.8% purity)

METHOD OECD TG 405 Acute Eye Irritation/Corrosion

Species/Strain Rabbit/Himalayan
Number of Animals 3 M
Observation Period 6 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	1.7	1.7	2	< 6 days	0
Conjunctiva: chemosis	0.3	1.7	1	2	< 6 days	0
Conjunctiva: discharge	-	-	-	-	-	-
Corneal opacity	0.3	0.3	1	2	< 3 days	0
Iridial inflammation	0.3	0.3	0.7	1	< 3 days	0

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

Remarks - Results

Moderate reddening of the conjunctivae (grade 2) was noted in all animals at the 1- and 24-hour observations which persisted up to 48 hours in two animals. Slight reddening (grade 1) persisted up to the 48-hour observation in one animal and up to the day 5 observation in the other two animals.

Slight chemosis (grade 1) was observed in all animals at the 1-hour observation and persisted up to 24 hours in one animal and up to 5 days in

another animal. Moderate chemosis (grade 2) was observed in the remaining animal at the 24 and 48 hour observation. Slight chemosis persisted in this animal for up to 5 days.

Slight to moderate corneal opacity was noted in all animals at the 24 hour observation and persisted up to 48 hours in one animal.

Slight iridial inflammation was observed in all animals at the 24 hour observation and persisted up to 48 hours in one animal.

All signs of irritation were resolved at the 6-day observation.

No abnormal body weight changes were observed during the study.

No clinical signs of systemic toxicity were observed.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY LPT (2004)

B.6. Skin sensitisation

TEST SUBSTANCE Notified chemical (98.5% purity)

METHOD OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test

Species/Strain Guinea pig/SPF

PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 0.625%
topical: 50%

MAIN STUDY

Number of Animals Test Group: 10 F Control Group: 5 F

Vehicle Intradermal: sunflower oil
Dermal: ethanol/diethylphthalate (1:1)

Positive control Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.

INDUCTION PHASE Induction Concentration:
intradermal: 1.25%
topical: 75%

Signs of Irritation Signs of skin irritation were observed and no further information, including type and intensity of reactions, was provided for the induction.

CHALLENGE PHASE

1st challenge topical: 50%

Remarks - Method A preliminary study was carried out to select suitable concentrations for induction and challenge.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge**	
		24 h	*48 h*	*24 h*	*48 h*
Test Group					
	50%	0	0	-	-
Control Group					
	50%	0	0	-	-

*Not conducted

Remarks - Results No mortality and no clinical signs of toxicity observed in the test animals, with all animals gaining weight during the study.

No signs of skin irritation were observed following challenge in the test

and control animals.

The positive control confirmed the sensitivity of the test system.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY FREY-TOX (2004b)

B.7. Skin sensitisation – modified mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical (93.9% purity)

METHOD Modified Local Lymph Node Assay (LLNA) (non-OECD guideline study)

Species/Strain	Mouse/albino SPF, female
Vehicle	Acetone/olive oil (4:1)
Preliminary study	No
Positive control	α-Hexylcinnamaldehyde (not conducted in parallel)
Remarks - Method	Non-radioactive method based on lymph node cell count. The method also incorporated the Integrated Model for the Differentiation of Skin reactions (IMDS) (Homey et al., 1998). The IMDS serves to distinguish between an inflammatory (non-specific) and an allergic (specific) reaction. A differentiation index (DI) based on lymph node cell count and ear swelling is calculated. A DI > 1 is considered an allergic reaction whereas a DI < 1 is considered an inflammatory response. On day 1, the thickness of ears was measured and 25 µL of the notified chemical or vehicle was topically applied to the dorsum of both ears for 3 consecutive days. On day 4, following measurement of ear thickness, the mice were euthanised and auricular lymph nodes were removed, their weights were recorded and lymph nodes cell suspensions were prepared by mechanical tissue disruption. The cell counts per millilitres of these suspensions were determined manually by Trypan blue exclusion using a NEUBAUER-chamber.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Lymph node cell count*	*Stimulation Index (Test/Control Ratio)*	*Differentiation Index*
Test Substance				
0 (vehicle control)	5 F	418	1.0	-
10	5 F	541	1.29	3.88
25	5 F	555	1.33	3.98
50	5 F	626	1.50	4.49

Remarks - Results The stimulation indices (SI) exceeded the positive threshold of 1.25 (as stated in the report for the strain of mice used in the study) for indicating a skin sensitisation potential at all test concentrations in a dose-related manner. No significant ear swelling indicating an inflammatory response was noted.

At all test concentrations the differentiation indices (DI) has exceeded in a dose-related manner the threshold of 1.00 for an allergic reaction. The study authors therefore concluded that the notified chemical was a skin sensitiser.

However, in the study a significant ear weight increase at all test concentrations in a non-dose dependent manner is noted which was not discussed in the study, but might be interpreted as a sign of non-immune tissue stimulation.

CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	FREY-TOX (2003c)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (93.9% purity)
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents
Species/Strain	Rat/CD/Crl:CD (SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	0.8% aqueous hydroxypropylmethyl-cellulose gel
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M/5F	0	0/10
low dose	5M/5F	100	0/10
mid dose	5M/5F	300	0/10
high dose	5M/5F	1,000	0/10
control recovery	5M/5F	0	0/10
high dose recovery	5M/5F	1,000	0/10

Mortality and Time to Death

No unscheduled mortalities observed during the study period.

Clinical Observations

Slight and slight to moderate salivation was observed in 8 animals (4M and 4F) treated at 300 mg/kg/ bw/day and all animals treated at 1,000 mg/kg bw/day immediately to 3 minutes after administration of the test substance and lasted up to 30 minutes. Salivation was observed from day 8 to day 28.

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

Laboratory Findings – Clinical Chemistry, Haematology

No treatment related changes on the haematological and biochemical parameters were noted.

Effects in Organs

Statistically significant and treatment related increase in relative and absolute liver weight (27% increase) was observed in males treated at all doses and females treated at 1,000 mg/kg bw/day. These findings, however, were not accompanied by associated clinical pathology or histopathological findings and thus were considered an adaptive response to the test substance.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established by the study authors as > 1,000 mg/kg bw/day in this study, based on the absence of toxicologically significant effects at any of the doses administered.

TEST FACILITY	LPT (2007b)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical (95.8% purity)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test

	Plate incorporation procedure (Test 1) and Pre incubation procedure (Test 2 and 2a)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102.
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	Test 1 a) With metabolic activation: 33 – 5,000 µg/plate b) Without metabolic activation: 33 – 5,000 µg/plate Test 2 and 2a a) With metabolic activation: 10 – 5,000 µg/plate b) Without metabolic activation: 10 – 5,000 µg/plate
Vehicle	Ethanol
Remarks - Method	A preliminary test at a concentration range of 3 – 5000 µg/plate was conducted with tester strains TA98 and TA100 only. The preliminary test was reported as part of main Test 1. Based on the results of Test 2, a pre-incubation study (Test 2a) was conducted with TA 98 without metabolic activation at a concentration range of 10 – 5,000 µg/plate (see Remarks – Results for further details). Negative control: ethanol Positive control: With metabolic activation: 2-aminoanthracene (all strains) Without metabolic activation: sodium azide (TA 1535 and TA 100), 4-nitro-o-phenylene-diamine (TA 1537 and TA 98), methyl methane sulfonate (TA 102). 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	≥ 2,500	≥ 2500	Negative
Test 2		≥ 2,500	≥ 333	Negative
Test 2a		≥ 333	≥ 1,000	Negative
Present				
Test 1	≥ 1,000	≥ 2,500	≥ 1,000	Negative
Test 2		≥ 100	≥ 33	Negative

Remarks - Results	Treatment related increase in revertant colonies was observed in TA 98 without metabolic activation in Test 2. The number of colonies reached or exceeded the threshold of twice the number of the corresponding solvent control at ≥ 2,500 µg/plate. To verify this result an additional experiment was performed as pre-incubation test with TA98 without metabolic activation (Test 2a). In this experiment an increase in revertant colonies was not observed, however, reduced background growth was observed at ≥ 333. Based on the results, the study authors asserted that the treatment related increase in revertant colonies in this strain in Test 2 was considered to be related to toxicity of the test substance rather than a possible mutagenic potential. For all other strains tested, no significant increases in the frequency of revertant colonies were observed, with any dose of the test substance, either with or without metabolic activation. The positive and negative controls gave a satisfactory response 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 (2005)

B.10. Genotoxicity – *in vitro* (chromosome aberration test)

TEST SUBSTANCE Notified chemical (88.5% purity)

METHOD OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain *Humans*
Cell Type/Cell Line Lymphocytes
Metabolic Activation System Phenobarbital/β-naphthoflavone induced rat liver
Vehicle Ethanol
Remarks - Method Negative control: ethanol
Positive control:
without metabolic activation – ethylmethane sulfonate
with metabolic activation - cyclophosphamide

The preliminary test fulfilled the requirements for cytogenic evaluation and thus served as Test 1.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	17.4, 30.4, 53.2*, 93.1*, 163.0*, 285.2, 499.1, 873.5, 1528.6 and 2675.0	4 h	22 h
Test 1a	1.0, 1.7, 3.0, 5.2, 9.1,16.0*, 28.0*, 49.0*,85.7 and 150.0	22 h	22 h
Test 2	0.6, 1.1, 1.9, 3.2, 5.7, 9.9*, 17.4*, 30.4*, 53.2 and 93.1	46 h	46 h
Present			
Test 1	17.4, 30.4, 53.2*, 93.1*, 163.0*, 285.2, 499.1, 873.5, 1528.6 and 2675.0	4 h	22 h
Test 2	53.2, 93.1*, 163.0*, 285.2, 499.1, 873.5, 1528.6* and 2675.0*	4 h	46 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 285.2	≥ 285.2	≥ 1528.6	Negative
Test 1a		≥ 49.0	> 150.0	Negative
Test 2		≥ 53.2	≥ 93.1	Negative
Present				
Test 1	> 2675.0	> 2675.0	≥ 163.0	Negative
Test 2		2675.0	≥ 2675.0	Negative

Remarks - Results In Test 1 and Test 1a (in the absence of S9-mix) cytotoxicity (29.8% and 30.7% respectively) was observed at 285.2 and 49.0 µL/mL, respectively. In Test 2 (in the presence of S9-mix), the highest concentration (2675.0 µL/mL) tested showed cytotoxicity (34.0%). In Test 2 (in the absence of S9-mix), 25.8% cytotoxicity was observed at 53.2 µL/mL. Slight to no cytotoxicity was observed at all other concentrations.

In both experiments, in the absence and presence of metabolic activation, no biologically relevant increase in structural chromosomal aberrations

	was observed. In Test 2 (in the presence of S9) a statistically significant increase in the number of aberrant cells, excluding gaps was observed at 1528.6 µg/mL. However the percentage of aberrant cells, excluding gaps at this concentration was lower than the historical control range of the test facility. Therefore the study authors considered the statistical significance to be biologically irrelevant. The positive controls behaved as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	RCC (2007)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from a municipal wastewater treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The measurement and recording of the oxygen demand was carried out continuously using a SAPROMAT respirometer (VOITH Inc.).
Remarks - Method	No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation (mean ± standard deviation)*	*Day*	*% Degradation*
14	63.7 ± 0.2	14	82.3 ± 3.8
28	79.6 ± 0.2	28	88.9 ± 4.3

Remarks - Results	The test was considered valid as all TG validity criteria were met. Toxicity control results showed that the test substance was not inhibitory at tested concentration of 100 mg/L. There was approximately 80% degradation of test substance in the static test after 28 days. Biodegradation within the 10-day-window, which started at day 3 was 62%. There was a clear two day lag or adaption phase. There was no noticeable abiotic degradation of the test substance after 28 days of incubation. Biodegradation of the test substance was over 60% within the 10-day-window.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	F-IMBAE (2005)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD analyser
Remarks - Method	No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Aniline*	
Day	*Cumulative % Degradation*	*Day*	*Cumulative % Degradation*
7	47	7	69
14	71	14	78
21	83	21	79
28	86	28	81

Remarks - Results	The test was considered valid as all TG validity criteria were met. Toxicity control results showed that the test substance was not inhibitory at tested concentration of 30 mg/L. There was approximately 86% degradation of the test substance in the test after 28 days. Cumulative percentage biodegradation within the 10-day-window (day 3 to 13) was 68%. Abiotic percentage degradation of the test substance was minimal (approximately 5%) relative to biodegradation within 28 days. Biodegradation of the test substance was over 60% within the 10-day-window.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	SRICITC (2013)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish
Species	*Danio rerio*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	57 – 65 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography-mass spectrometry (GC-MS)
Remarks – Method	No significant deviations from the test guidelines were reported. There was no information provided on whether the test substance was fully dissolved in the test solution.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	0	7	0	0	0	0	0
0.60	0.28	7	0	0	0	0	0

LC50	> 0.28 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The measured test substance concentrations ranged from 0.83 to 0.45 mg/L (geo. mean = 0.60 mg/L) in fresh test solutions and 0.15 to 0.27 mg/L in 24-h old solutions. Because the 24-h old solutions were < 80% of the fresh solution concentration. Therefore, the geometric mean measured concentration was used. No mortalities of *Danio rerio* were observed in either the control or treated group. However, there were some behavioural effects seen in the exposed group over the testing period. There was no statistical analysis to evaluate whether these behavioural effects were significant. Slow-escape reflex appeared to decrease with exposure and hyperventilation was only seen (for all fish) at 2 h exposure to the test substance.
CONCLUSION	The notified chemical is not toxic to the limits of water solubility.
TEST FACILITY	UN-Lab (2008a)

C.2.2. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Closed, semi-static EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish
Species	*Gobiocypris rarus*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	130 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography- Flame Ionization Detector (GC-FID)
Remarks – Method	No significant deviations from the test guidelines were reported. There was no information provided on whether the test substance was fully dissolved in the test solution.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
Control	0	7	0	0	0	0
0.5	0.138	7	0	0	0	0
0.59	0.173	7	0	0	0	0
0.71	0.223	7	0	0	0	0
0.84	0.281	7	0	0	0	0
1.0	0.349	7	0	0	0	0

LC50	> 0.35 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The mean measured concentrations in old solutions were 31.0 - 42.2% of the corresponding mean measured concentrations in freshly prepared solutions, respectively. Therefore, the geometric mean measured concentration was used. No mortalities of *Gobiocypris rarus* were observed in either the control or treated group.
CONCLUSION	The notified chemical is not toxic to the limits of water solubility.
TEST FACILITY	SYRICI (2007)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-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	231.4 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography- Flame Ionization Detector (GC-FID)
Remarks - Method	No significant deviations from the test guidelines were reported. Stock solutions for the test were clear upon visual inspection. However, initial loading (including analytical verification) indicate that the test substance was present at levels in excess of the water saturation limit for each of the test concentrations. A control (test medium of dechlorinated drinking water and deionised water) and solvent control (0.1 mL acetone/L medium) were included in the test design. Two concentrations of the reference substance potassium-dichromate (0.9 and 1.9 mg/L) were also tested.

Results

Concentration mg/L		Number of D. magna	Number Immobilised	
Nominal	Actual		24 h	48 h
Control	0	20	0	0
Solvent control (acetone)	0	20	0	0
0.40	0.189	20	0	0
0.64	Not reported (nr)	20	0	0
1.02	0.461	20	0	0
1.64	0.716	20	0	1
2.62	nr	20	0	4
4.19	nr	20	0	5
6.71	nr	20	0	3
10.7	0.853	20	0	7

EC50 > 0.85 mg/L at 48 hours

Remarks - Results All validity criteria for the test were satisfied. Over time the test substance concentrations decreased to ~40% of initial concentrations during each 24-hour renewal interval. Therefore, toxicity endpoints are based on mean measured concentrations. Mean measured concentrations were based on samples taken at 0, 24 and 48 hours of fresh and aged test solutions.
No immobilisation was observed in the control or the solvent control.

The 48 h EC50 for the reference substance (potassium dichromate) was not reported other than stating that it was within the range of two concentrations tested (0.9 mg/L and 1.9 mg/L).

No immobilisation occurred at the test groups up to a nominal concentration of 1.02 mg/L (mean measured concentrations of 0.461 mg/L). There was a clear dose-response relationship in the test groups, with 5 to 35% immobilisation of the test organisms observed at higher test concentrations. However, it is also possible that the immobilisation observed was due to physical adhesion to an oily film on the test solution surface.

The 48 h EC50 was determined to be > 0.85 mg/L (measured), because less than 50% immobilisation was observed up to the highest concentration tested, which is just below the water solubility for the notified chemical is 0.982 mg/L at 20 °C. The observed mortality may not be related to toxicity of the test substance, but rather due to a physical effect.

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

TEST FACILITY GAB (2005b)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
EC Council Regulation No 440/2008 C.3 Algal Inhibition Test

Species *Desmodesmus subspicatus*
Exposure Period 72 hours
Concentration Range Nominal: 0.912 mg/L (saturated solution, measured at test start without algae)
Actual: 0.890 mg/L (saturated solution, measured at test start without algae, see comments on method)
Auxiliary Solvent None
Water Hardness The test medium nominal hardness was 0.24 mmol Ca and Mg/L.
Analytical Monitoring Gas chromatography- tandem mass spectrometry (GC-MS/MS)

Remarks - Method	No significant deviations from the test guidelines were reported. Based on the results of a preliminary range finding test, a test was performed with a limit concentration (six replicates). Replicates of test solutions without algae were used for test substance analysis after 72 hours. The recovery was above 80% of the initial measured concentration after 72 hours in the test vessel without algae, i.e., saturated solution (1:1) without algae 0.912 and 0.890 at start and end of test, respectively. Therefore all effect values are given based on initial measured concentrations of the test substance. However, the solution with test substance at saturation and algae after 72 hours was 0.423 mg/L. The solution with test substance at saturation and algae was not measured at the start of the test. The toxicity of potassium dichromate to the unicellular freshwater green alga *Desmodesmus subspicatus* was determined over a period of 72 hours at the same time that the test substance was tested.

RESULTS

Yield inhibition EyC50 mg/L at 72 h	*Growth rate inhibition ErC50 mg/L at 72h*
> 0.91 (95% confidence interval: could not be determined)	> 0.91 (95% confidence interval: could not be determined)

Remarks - Results	All validity criteria for the test were satisfied. The results of the limit test, which was performed with the saturated solution were reported. No effects on the growth of the freshwater green alga *Desmodesmus subspicatus* were observed in the saturated test substance solution treatment. The 72 h EyC50 and the ErC50 (95% confidence intervals) for the toxic reference substance (potassium dichromate) was 0.42 (0.37 – 0.48) and 1.01 (0.90 – 1.1) mg/L, respectively.
CONCLUSION	The notified chemical is not toxic to the limits of water solubility.
TEST FACILITY	UN-Lab (2008b)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge
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 under static conditions with the nominal concentration 1,000 mg/L (nominal), chosen based on the results of a range-finding test. The test substance was not measured over the duration of the test. Copper (II) sulphate pentahydrate was used instead 3,5-dichlorophenol as the reference substance. The test range for this reference substance (53 – 157 mg/L) was based on a mean of tests from 1991 – 2007 and was similar to that recommended in the TG 209 (53 – 155 mg/L).
RESULTS	
IC50	1,000 mg/L
Remarks – Results	All validity criteria for the test were satisfied. There was 16% inhibition in

	the test substance treatment and no inhibition in the two controls. The EC50 of the reference substance was 101 mg/L. The test substance is not considered to significantly affect metabolism of wastewater treatment microorganisms at a concentration of 1,000 mg/L.
CONCLUSION	Not inhibitory to microbial respiration.
TEST FACILITY	UN-Lab (2009)

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