File No: LTD/2006

February 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Ethanone, 1-(2-benzofuranyl)-

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:

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Director
NICNAS

TABLE OF CONTENTS

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2006	Symrise Pty Ltd	Ethanone, 1-(2-benzofuranyl)-	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

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 3	H402 - Harmful to aquatic life

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

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

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

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

- 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 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 0.10% in fine fragrances, 0.13% in face cream, 0.14% in hand cream, 0.35% in other cosmetic products or 0.05% in household cleaning products;
- information becomes available on the repeated dose toxicity of the notified chemical;

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
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)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH, adsorption/desorption, dissociation constant and autoignition temperature.

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

NOTIFICATION IN OTHER COUNTRIES
Philippines (2014)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Coumarone

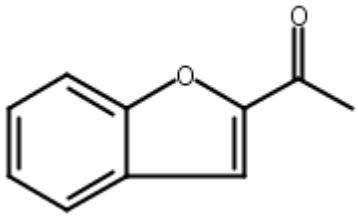
CAS NUMBER
1646-26-0

CHEMICAL NAME
Ethanone, 1-(2-benzofuranyl)-

OTHER NAMES
1-(Benzofuran-2-yl)ethanone

MOLECULAR FORMULA
$C_{10}H_8O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
160.18 g/mol

ANALYTICAL DATA
Reference NMR, IR, GC, GC-MS, and UV-Vis 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 to beige crystals

Property	Value	Data Source/Justification
Melting Point	70.7 °C	Measured
Boiling Point	270.0 °C at 101.3 kPa	Measured
Density	1,305 kg/m^3 at 20 °C	Measured
Vapour Pressure	2.6×10^{-4} kPa at 25 °C	Measured
Water Solubility	453 mg/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain readily hydrolysable functionality
Partition Coefficient (n-octanol/water)	log P_{ow} = 1.94 at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.19	Calculated using log P_{ow} method, KOCWIN v2.00, US EPA EPI Suite
Dissociation Constant	Not determined	Does not contain dissociable functionality
Particle Size	Inhalable fraction (< 100 μm): ~39.5% Respirable fraction (< 10 μm): ~4.3% MMAD = 148.7 μm	Measured
Flash Point	Not determined	The notified chemical is a solid
Flammability	Not readily combustible	Measured
Autoignition Temperature	Not determined	Not expected to autoignite under normal conditions of use.
Explosive Properties	Not determined	Contain no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contain no functional groups that would imply oxidising properties

* MMAD = Mass Median Aerodynamic 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 in the neat form, as a component of fragrance oil at < 15% concentration or as a component of finished cosmetic and household products at ≤ 0.35% concentration.

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

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

PORT OF ENTRY

Sydney

IDENTITY OF RECIPIENTS

Symrise Australia

TRANSPORTATION AND PACKAGING

The notified chemical in the neat form will be imported in closed 20 kg cardboard cartons with blue plastic inner bags. The fragrance oils containing the notified chemical at < 15% concentration will be imported in 30 L and 216 L tightly closed lacquered metal drums and 30 L HDPE/EVOH canisters. The finished cosmetic and household products containing the notified chemical at ≤ 0.35% 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	0.1
Face cream	0.13
Hand cream	0.14
Other cosmetic products	0.35
Household cleaning products	0.05

OPERATION DESCRIPTION

Reformulation

Reformulation of the notified chemical or fragrance oils containing the notified chemical in its neat form or at < 15% concentration into finished cosmetic and household products 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

Household cleaning products

Finished household cleaning products containing the notified chemical at ≤ 0.05% concentration will be used by consumers and professional cleaners. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines or open processes, and manually applied by sponge, mop, spray or brush followed by wiping or rinsing.

Cosmetics

The finished cosmetic products containing the notified chemical at ≤ 0.35% 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 workers	None	Incidental
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	0.5	2
Packaging	4	2
Professional end users (beauticians, cleaners, etc)	1-8	200

EXPOSURE DETAILS

Transport and storage

Transport, storage and warehouse workers may come into contact with the notified chemical in the neat form or at < 15% concentration in fragrance oils or at ≤ 0.35% 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 < 15% 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 ≤ 0.35% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers and workers in beauty salons), 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

Public exposure to the notified chemical is expected to be widespread and frequent through daily use of cosmetic and household cleaning products containing the notified chemical at ≤ 0.35% concentration. The principal route of exposure will be dermal, while ocular and inhalation exposure (e.g. through the use of spray products) are also possible.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemicals may be used are shown in the following tables (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 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	0.350	1	0.4277
Face cream	1540	0.130	1	0.0313
Hand cream	2160	0.140	1	0.0473
Fine fragrances	750	0.100	1	0.0117
Deodorant spray	1430	0.350	1	0.0820
Shampoo	10460	0.350	0.01	0.0057
Conditioner	3920	0.350	0.01	0.0021
Shower gel	18670	0.350	0.01	0.0102
Hand soap	20000	0.350	0.01	0.0109
Hair styling products	4000	0.350	0.1	0.0219
Total				**0.6508**

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	0.05	0.95	10	0.0017
Fabric softener	90	0.05	0.95	10	0.0007
Total					**0.0024**

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	0.05	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.05	1980	0.009	0.01	0.03	0.0001
All-purpose cleaner	1	0.05	1980	1	0.01	0.007	0.0011
Total							**0.0012**

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	0.35	20	1	20	50	1	10	**0.0113**

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. This would result in a combined internal

dose of 0.6657 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.

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	not irritating
Eye irritation *in vitro* Bovine Corneal Opacity Test (BCOP)	not irritating
Guinea pig, skin sensitisation – adjuvant test	evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation (EC3 = 3.3%)
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation at up to 30% concentration
Human, skin sensitisation – RIPT	no evidence of sensitisation at 10% concentration
Mutagenicity – bacterial reverse mutation	non mutagenic
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics

Absorption across the skin, gastrointestinal tract and respiratory tract is expected based on the low molecular weight (160.18 g/mol), low partition coefficient (Log Pow = 1.94) and moderate water solubility (453 mg/L at 20 °C) of the notified chemical.

Acute toxicity

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

In the acute oral toxicity study, two males out of 10 animals exposed to 2,000 mg/kg bw of the notified chemical died on day 2 of the observation and these animals showed haemorrhagic lungs, dark liver and dark kidneys at necropsy.

Irritation and sensitisation

Based on a study conducted in rabbits, the notified chemical is not irritating to the skin.

In an *in vitro* bovine corneal opacity and permeability (BCOP) test the notified chemical was determined to be not irritating to eyes.

Sensitisation

Three animal sensitisation studies (one guinea pig maximization test [GPMT] and two mouse local lymph node assays [LLNA]) and one human repeat insult patch test [HRIPT]) were provided for the notified chemical.

In the GPMT, the notified chemical was found to be sensitising. During challenge at 25% concentration irritation was observed in 12/20 animals at the 24 hour observation and 13/20 animals at the 48 hour observation. No signs of irritation were noted in the control animals.

In one LLNA study, the notified chemical was found not to be sensitising with stimulation indices of 0.78, 1.34 and 0.64 at 1%, 10% and 30%, respectively. However in the second LLNA study, the notified chemical was determined to be a skin sensitiser with stimulation indices of 2.06, 5.77 and 5.87 at 1%, 10% and 30%, respectively. The EC3 value was calculated to be 3.3%.

In the HRIPT the notified chemical was not a skin sensitiser when tested at 10% concentration with 49 subjects completing the study. Slight to moderate skin reactions in seven subjects were observed during the induction phase (second and third week) and no reactions were noted in subjects during the challenge phases.

Based on the results of the GPMT and LLNA, the notified chemical is considered to be a skin sensitiser.

Mutagenicity/Genotoxicity
The notified chemical was negative in two bacterial reverse mutation tests.

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

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 sensitiser.

Reformulation
During reformulation, workers may be exposed to the notified chemical at ≤ 100% 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 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 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 ≤ 0.35% 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 ≤ 0.35% concentration through daily use of cosmetic and household products. The main route of exposure is expected to be dermal and inhalation, with some potential for accidental ocular or oral exposure.

Sensitisation
Based on the results of an LLNA study the notified chemical is a skin sensitiser with an EC3 value of 3.3%.

Proposed methods for the quantitative risk assessment of the dermal sensitisation have been the subject of significant discussion (i.e., Api *et al.,* 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in cosmetic and household products may be estimated (SCCS, 2012 and Cadby *et al*, 2002). Based on the EC3 value derived from the LLNA study and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 3.59 µg/cm^2/day. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300.

Product type	**Proposed usage concentration (%)**	**CEL (µg/cm^2)**	**AEL (µg/cm^2)**	**Allowable concentration (%)**
Fine fragrances	0.10	3.75	3.59	0.10
Face cream	0.13	3.54	3.59	0.13
Hand cream	0.14	3.52	3.59	0.14
Other rinse-off and leave-on cosmetics (assumed body lotion)	0.35	1.75	3.59	0.72
Household product	0.05	0.09	3.59	2.09

(assumed cleaning liquid)

As the AEL ≥ CEL (apart for fine fragrances where the AEL is slightly lower than the CEL but is considered acceptable), the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at ≤ 0.10% concentration in fine fragrances, ≤ 0.13% concentration in face cream, ≤ 0.14% concentration in hand wash soap, ≤ 0.35% concentration in other rinse-off and leave-on cosmetic products (using body lotion as a worst case example) and ≤ 0.05% concentration in household products (using cleaning liquid as a worst case example) is not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Repeated-dose toxicity
The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low concentrations of the notified chemical in end use products (≤ 0.35%).

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.10% in fine fragrances, ≤ 0.13% in face cream, ≤ 0.14% in hand cream, ≤ 0.35% in other cosmetic products and ≤ 0.05% in household cleaning products, is not considered to be unreasonable. In the absence of data on the repeated dose toxicity potential of the notified chemical, use of the notified chemical is supported only under limited exposure conditions, which are reflected in the low concentrations of the notified chemical in end-use products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported into Australia as a component of end-use cosmetic and household products, or in either the neat form or as a component of fragrance solutions for reformulation into the end-use products. In general, the reformulation processes are expected to involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into end-use containers. Liquid waste from cleaning of the reformulation equipment will either be reused or disposed of through an approved waste management facility. Release of the notified chemical to the environment in the event of accidental spills or leaks during reformulation, storage and transport is expected to be collected for disposal to landfill in accordance with local government regulations. Empty import containers containing residue notified chemical will either be recycled or disposed of through an approved waste management facility.

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

RELEASE OF CHEMICAL FROM DISPOSAL
Residues of the notified chemical in empty end-use containers are likely to either share the fate of the containers and be disposed of to landfill, or be released to the sewer system when the containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate
Based on its use as a component of cosmetic and household products, the majority of the notified chemical is expected to be released to sewers, and then to sewage treatment plants (STPs) before potential release to surface waters. Based on its moderate water solubility (453 mg/L) and low log P_{ow} (log P_{ow} = 1.94), the majority of the notified chemical is expected to present in the water phase in STPs. A ready biodegradability study conducted on the notified chemical shows that it is readily biodegradable (75% degradation after 28 days). Therefore, the notified chemical is expected to be removed effectively by biodegradation at STPs, and only a very small proportion of the notified chemical will be released to surface waters after STPs. For details of the biodegradability study, please refer to Appendix C. A small proportion of the notified chemical may adsorb to sludge in STPs. The waste sludge containing the notified chemical will be sent to landfill for disposal or agricultural land for remediation. A minor amount of the notified chemical may also be disposed of to landfill as

collected spills and empty container residues. The notified chemical is expected to have moderate mobility in soil based on its predicted log K_{oc} of 2.19. The notified chemical is not expected to significantly bioaccumulate in biota based on its ready biodegradability and low log P_{ow}. In landfill, sludge and water, the notified chemical is expected to undergo degradation by biotic and abiotic processes, eventually forming 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. It is also assumed under the worst-case scenario that there is no 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	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.74 µg/kg.

7.2. Environmental Effects Assessment

The results from Daphnia ecotoxicity and algal ecotoxicity studies conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix C. As measured fish ecotoxicity was not available, the endpoint was estimated using ECOSAR v1.10 (US EPA, 2012).

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h) = 149 mg/L	Not expect to be harmful to fish
Daphnia Toxicity	EC50 (48 h) = 32 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	ErC50 (72 h) = 40 mg/L	Harmful to alga

Based on the above measured endpoints for Daphnia and alga, the notified chemical is expected to be harmful to aquatic organisms under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). Therefore, the notified chemical is formally classified as “Acute Category 3; Harmful to aquatic life” under the GHS (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated based on the most sensitive endpoint for Daphnia as shown in the table below. A conservative assessment factor of 1000 was used given the measured acute endpoint for only two trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Daphnia EC50	32	mg/L
Assessment Factor	1,000	
Mitigation Factor	1	
PNEC:	32	µg/L

7.3. Environmental Risk Assessment

Based on the above predicted PEC and PNEC, the following Risk Quotient (Q = PEC/PNEC) has been calculated.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	32	**0.018**
Q - Ocean	0.06	32	**0.002**

The conservative risk quotient for discharge of effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. Based on its ready biodegradability and low log P_{ow}, the notified chemical is not expected to be bioaccumulative. Therefore, on the basis of the predicted PEC/PNEC ratio, the maximum annual importation volume, and the assessed use pattern as a component of cosmetic and household products, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 70.7 °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	Consilab (2017a)

Boiling Point 270.0 °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	Consilab (2017a)

Density 1,305 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	Consilab (2017b)

Vapour Pressure 2.6×10^{-4} 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	Consilab (2017c)

Water Solubility 453 mg/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Flask Method
Test Facility	IES (2017a)

Partition Coefficient (n-octanol/water) $\log P_{ow} = 1.94$ at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method
Test Facility	IES (2017b)

Particle Size Mass median diameter (MMD) 148.7 µm

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

Median Diameter	*Particle Size (µm)*
D_{90}	690.7
D_{50}	148.7
D_{10}	25.2

Remarks	Determined by laser diffraction method.
Test Facility	Consilab (2017d)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids) UN Recommendations on the Transport of Dangerous Goods
Remarks	The notified chemical could not be ignited with a flame for at least 2 minutes. The product

	has not to be classified as readily combustible solid in class 4.1 according to the UN Transport Regulation.
Test Facility	Consilab (2017e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 401 Acute Oral Toxicity (1987)
Species/Strain	Rat/Sprague-Dawley CD
Vehicle	Dimethyl sulphoxide
Remarks - Method	Based on the results of a range finding study, 2,000 mg/kg bw was chosen for main study. No protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	Two males were found dead on day 2. Ataxia, hunched posture, lethargy, decreased respiratory rate or laboured respiration with additional signs of ptosis, increased salivation and red/brown stains around the mouth or snout were observed in all animals at the 30 minute observation. At the day 2 observation, all three surviving males showed hunched posture and reduced respiration rate. In addition, one male showed laboured respiration and another male showed lethargy. Hunched posture was observed in all three males up to day 4 or 5. One male showed ataxia up to day 4 and another two males showed decreased respiratory rate at days 3 and 4 of the observation. Hunched posture was observed in all females up to days 2 or 3. All surviving animals had recovered at day 6.
Effects in Organs	Haemorrhagic lungs, dark liver and dark kidneys were observed at necropsy of the two males that died during the study. No abnormalities were noted at necroscopy in surviving animals.
Remarks - Results	Surviving animals showed expected body weight gain during the study except for one female which showed bodyweight loss during the first week and expected body weight gain in the second week.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	SafePharm (1996a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (99.9% purity)
METHOD	OECD TG 402 Acute Dermal Toxicity (1987)
Species/Strain	Rat/Sprague-Dawley CD
Vehicle	Moistened with distilled water
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 signs of toxicity were observed.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed.
Effects in Organs	No abnormalities were observed during necroscopy.
Remarks - Results	All treated animals showed expected body weight gain during the study period.

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

TEST FACILITY SafePharm (1996b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical (99.9% purity)

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion (1992)

Species/Strain	Rabbit/New Zealand White/SPF
Number of Animals	4F
Vehicle	Ethanol and diethyl phthalate (1:1)
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	Animals were treated with 1%, 5%, 10%, 25% and 100% of the notified chemical. No protocol deviations.

RESULTS

Remarks - Results	No signs of irritation were noted at 100% concentration of the notified chemical. One animal treated at 1%, 5%, 10% and 25% of the notified chemical showed very slight erythema (score 1) at the day 1 observation. Symptoms persisted up to day 2 of the observation treated at 10% and 25% of the notified chemical. All signs of irritation were resolved at the 72 hour observation.

CONCLUSION The notified chemical is not irritating to the skin.

TEST FACILITY Scantox (1996a)

B.4. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical (100% purity)

METHOD OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (2013)

Vehicle	Saline
Remarks - Method	Positive and negative controls were run in parallel with the test substance: - Negative control: saline (0.9% NaCl in deionised water) - Positive control: 10% (w/v) benzalkonium chloride in 0.9% saline

Standard deviation values were not provided. No significant protocol deviations.

RESULTS

Test material	*Mean opacities of triplicate tissues*	*Mean permeabilities of triplicate tissues*	*IVIS*
Vehicle control	0.33	0.063	1.28
Test substance	-0.33*	0.033*	0.16
Positive control	115.31*	0.1*	116.83

IVIS = *in vitro* irritancy score
*Corrected for background values

Remarks - Results

A mean *in vitro* irritancy score of 0.16 was obtained for the test substance. The test substance is therefore not considered to be corrosive or a severe eye irritant.

The positive and negative controls gave satisfactory results confirming the validity of the test system.

CONCLUSION

The notified chemical is not irritating to the eye under the conditions of the test.

TEST FACILITY

Envigo (2017a)

B.5. Skin sensitisation – Guinea pig maximization test (GPMT)

TEST SUBSTANCE

Notified chemical (99.9% purity)

METHOD

OECD TG 406 Skin Sensitisation – GPMT (1992)

Species/Strain

Guinea pig/SPF/Dunkin Hartley

PRELIMINARY STUDY

Maximum Non-irritating Concentration:
intradermal: < 1.25%
topical: 25%

MAIN STUDY

Number of Animals

Test Group: 20F Control Group: 10F

Vehicle

Sesame oil for intradermal induction
Ethanol:diethylphthalate (1:1) for topical induction and challenge application.

Positive control

Not stated

INDUCTION PHASE

Induction Concentration:
intradermal: 10%
topical: 25%

Signs of Irritation

Intradermal injections of Freund's complete adjuvant with vehicle or test substance elicited irritation. No skin reactions were observed following topical induction with either the test substance or vehicle.

CHALLENGE PHASE

1st challenge

topical: 25%

Remarks - Method

In the preliminary intradermal irritancy study, both exposed animals showed slight erythema at the 24 hour and 48 hour observations at both concentrations (1.25% to 10%) tested. No skin reactions were observed in both animals in the preliminary topical irritancy study conducted at 6.25% to 25% concentration of the test item.

Intradermal induction was conducted on day 1, topical induction on day 8 and topical challenge on days 22 - 23. All animals at the control and test group were pre-treated with 0.5 g of sodium lauryl sulphate (10% in petrolatum) on test day 7.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	25%	12/20	13/20
Control Group	25%	0/10	0/10

Remarks - Results

There were no deaths or substance-related signs of toxicity during the study.

Two animals showed slight or discrete erythema and 10 animals showed moderate and confluent erythema at 24 hour challenge observation.

At 48 hour challenge observation, 4 animals showed slight or discrete erythema, 7 animals showed moderate and confluent erythema and 2 animals showed intense erythema.

Normal body weight gains were recorded for all animals during the course of the study.

CONCLUSION

There was evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY

Scantox (1996b)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA) (1)

TEST SUBSTANCE

Notified chemical (99.9% purity)

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (1992)

Species/Strain: Mouse/CBA/Ca/Hsd

Vehicle: Acetone

Preliminary study: No

Positive control: Not conducted in parallel with the test substance, but had been conducted at approximately 6 months intervals previously in the test laboratory using hexylcinnamaldehyde.

Remarks - Method

A pre-screen test was not conducted to justify the dose concentrations.
The study was conducted in male animals rather than females as stated in the test guideline.
Acetone is not one of the recommended vehicles under the test guideline.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4M	121	-
1	4M	94	0.78
10	4M	162	1.34
30	4M	78	0.64
Positive Control			
Vehicle control	4M	45	-
1	4M	118	2.62
3	4M	365	8.11
10	4M	4.81	10.69

Remarks - Results

Information on signs of irritation or systemic toxicity in the test and control animals was not provided.

The test substance did not elicit a stimulation index (SI) ≥ 3 at any test dose concentration. A dose response was not observed.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical at up to 30% concentration.

TEST FACILITY ZENECA (1997a)

B.7. Skin sensitisation – mouse local lymph node assay (LLNA) (2)

TEST SUBSTANCE Notified chemical (99.9% purity)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/Ca
Vehicle Acetone
Preliminary study No
Positive control Not conducted in parallel with the test substance, but had been conducted at approximately 6 months intervals previously in the test laboratory using hexylcinnamaldehyde. The positive control study included in the report was the study conducted closer in time to the main study.
Remarks - Method A pre-screen test was not conducted to justify the dose concentrations.
The study was conducted on male animals rather than females as stated in the test guideline.
Acetone is not one of the recommended vehicles under the test guideline.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4M	53	-
1	4M	109	2.06
10	4M	306	5.77
30	4M	311	5.87
Positive Control			
Vehicle control	4M	116	-
1	4M	288	2.48
3	4M	621	5.35
10	4M	923	7.96

EC3 3.3
Remarks - Results No unscheduled mortalities or signs of systemic toxicity were observed during study period.

The stimulation index was > 3 in the 10% and 30% test groups, indicating a sensitising response. The EC3 was calculated to be 3.3%.

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

TEST FACILITY ZENECA (1997b)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (99.9% purity) at 10% concentration

METHOD Repeated insult patch test with challenge
Study Design Induction Procedure: 50 µL test substance was applied under an occlusive patch 3 times per week (Monday, Wednesday and Friday) for a total of 9

	applications. Patches were removed after 48 h and graded (6 h after the removal of patches) after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 14 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed after 48 h. Sites were graded 48, 72 and 96 h after application.
Study Group	36F, 14M; age range 23 to 68 years
Vehicle	Ethanol/diethyl phthalate (1:1)
Remarks - Method	Occluded. Patch sizes used in the study were not provided. Positive and negative controls, conducted in humans, were run in parallel with the test substance: - Negative control: deionised water - Positive control: 0.05% sodium dodecylsulfate (0.3% aqueous solution)
RESULTS	
Remarks - Results	Forty-nine out of 50 subjects completed the study. One subject did not take part in the challenge phase for reasons unrelated to the test substance. In week 2 five slight reactions and one moderate reaction of erythema was noted in five subjects. In week 3 six slight reactions in four subjects were noted. In all skin reactions were observed in 7/50 subjects during the induction phase. No adverse responses were noted at challenge phase. The positive controls behaved as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical at 10% concentration was non-sensitising under the conditions of the test.
TEST FACILITY	Institute Dr. K. Schrader (1998)

B.9. Genotoxicity – bacteria (1)

TEST SUBSTANCE	Notified chemical (100% purity)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Plate incorporation method (Test 1) Pre-incubation method (Test 2)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98 and TA100. *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	<u>Test 1</u> a) With metabolic activation: 3 – 5,000 µg/plate b) Without metabolic activation: 3 – 5,000 µg/plate <u>Test 2 (TA1535 and TA100)</u> a) With metabolic activation: 33 – 5,000 µg/plate b) Without metabolic activation: 33 – 5,000 µg/plate <u>Test 2 (all other strains)</u> a) With metabolic activation: 10 – 5,000 µg/plate b) Without metabolic activation: 10 – 5,000 µg/plate
Vehicle	Dimethyl sulfoxide (DMSO)
Remarks - Method	Negative and positive controls were used in parallel with the test material. Negative control: DMSO Positive control: i) with S9-mix: 2-aminoanthracene and ii) without S9-mix: Sodium azide (TA100 and TA1535); 4-nitro-phenylendiamine

(TA98 and TA1537); and methyl methane sulfonate (WP2uvrA).
The preliminary toxicity test served as the main test and reported as Test 1.

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	Negative
Test 2		≥ 2,500	> 5,000	Negative
Present				
Test 1	> 5,000		≥ 5,000	Negative
Test 2		≥ 1,000	> 5,000	Negative

Remarks - Results

In Test 1 (plate incorporation method), the test substance caused no visible reduction in the growth of the bacterial background lawn at any dose tested (both with and without S9-mix).

In Test 2 (pre-incubation method), without S9-mix, reduced background growth was observed in TA1537 at ≥ 2,500 μg/plate and in TA1535 and TA100 at 5,000 μg/plate. Reduced background growth was observed in TA98 and TA100 at ≥ 1,000 and for TA1535 and TA1537 at ≥2,500 with S9-mix.

No substantial increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose level either with or without metabolic activation or exposure method.

The vehicle control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY

Envigo (2017b)

B.10. Genotoxicity – bacteria (2)

TEST SUBSTANCE

Notified chemical (99.6% purity)

METHOD

Similar to OECD TG 471 Bacterial Reverse Mutation Test
Plate incorporation method

Species/Strain: *Salmonella typhimurium*: TA1535, TA1537, TA1538, TA98 and TA100.
Metabolic Activation System: S9 mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test: a) With metabolic activation: 50 – 5,000 μg/plate
b) Without metabolic activation: 50 – 5,000 μg/plate
Vehicle: Dimethyl sulfoxide (DMSO)
Remarks - Method: Negative and positive controls were used in parallel with the test material.

Negative control: DMSO
Positive control: i) with S9-mix: 2-aminoanthracene and ii) without S9-mix: Sodium azide (TA100 and TA1535); 2-nitrofluorene (TA98 and TA1538); and 9-aminoacridine (TA1537).

An *E.coli* bacterial strain was not included.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	Not conducted	≥ 1,500	> 5,000	Negative
Test 2		≥ 1,500	> 5,000	Negative
Present				
Test 1	Not conducted	≥ 5,000	> 5,000	Negative
Test 2		≥ 5,000	> 5,000	Negative

Remarks - Results

In Tests 1 and 2 without metabolic activation, the test material was toxic to TA1537 strain at ≥ 1,500 µg/plate.

The test substance caused a visible reduction in the growth of the bacterial background lawn to all strains, at ≥ 5,000 µg/plate with metabolic activation.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose level either with or without metabolic activation.

All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY

Freiburger Labor für Mutagenitatsprufung (1996)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical (100% purity)
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from a local STP
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Oxygen consumption by OxiTop® system
Remarks - Method	No significant deviation from the test guidelines was reported. The test substance was added directly to the culture bottles with dilution water to achieve a concentration of 25 mg/L. A toxicity control was run.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	0	7	82
14	9	14	90
21	63	21	95
28	75	28	95

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 60% within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The 10 day window started by day 14th with the mean degradation of 9% and finished by day 23rd with the mean degradation of 66%. The degree of degradation of the notified chemical after 28 days was 75%.
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Dr U Noack-Laboratorien (2011)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (100% 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 - Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	High Performance Liquid Chromatography-UV detection (HPLC-UV)
Remarks - Method	No significant deviation from the test guidelines were reported. The highest test concentration of 100 mg/L was prepared by directly adding the test substance to the dilution water. Other test concentrations were achieved by further dilution of the 100 mg/L concentration solution. The

actual test concentrations were measured at the start and at the end of the test, and found to be stable.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	<LOQ[a]	20	0	0
10	9.77	20	0	0
22	21.7	20	0	0
46	45.4	20	2	20
100	97.3	20	20	20

[a]LOQ: Limit of Quantitation of 0.08 mg/L based on calibration standards

EC50 32 (95% CL of 22-46) mg/L at 48 hours (calculated using the geometric mean value of consecutive EC_0 and EC_{100}).

Remarks - Results All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is harmful to aquatic invertebrates.

TEST FACILITY IES (2017c)

C.2.2. Algal growth inhibition test

TEST SUBSTANCE Notified chemical (100% purity)

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

Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 0.32, 1.0, 3.2, 10, 32, 100 mg/L
Actual: <LOQ[a], 3.08, 9.84, 31.5, 97.5 mg/L
Auxiliary Solvent None
Water Hardness 15 mg $CaCO_3$/L
Analytical Monitoring High Performance Liquid Chromatography-UV detection (HPLC-UV)
Remarks - Method No significant deviation from the test guidelines were reported. The highest test concentration of 100 mg/L was prepared by directly adding the test substance to the dilution water. Other test concentrations were achieved by further dilution of the 100 mg/L concentration solution. The actual test concentrations were measured at the start and at the end of the test, and found to be stable.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
40 (95% CL of 37-46)	3.2	18 (95% CL of 17-20)	3.2

Remarks - Results All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is harmful to alga.

TEST FACILITY IES (2017d)

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