File No: LTD/1937

January 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4*H*-4a,9-Methanoazuleno[5,6-*d*]-1,3-dioxole, octahydro-2,2,5,8,8,9a-hexamethyl-, (4a*R*,5*R*,7a*S*,9*R*)-

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

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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/1937	Symrise Pty Ltd	4*H*-4a,9-Methanoazuleno[5,6-*d*]-1,3-dioxole, octahydro-2,2,5,8,8,9a-hexamethyl-, (4a*R*,5*R*,7a*S*,9*R*)-	Yes	≤ 0.8 tonne/s 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
Serious Eye Damage/Eye irritation (Category 2)	H319 – Causes serious eye irritation

Human health risk assessment
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 corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Serious Eye Damage/Eye irritation (Category 2): H319 – Causes serious eye 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
  - Exhaust ventilation

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

- 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, goggles

  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.

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 0.8% in end-use products

or

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from a fragrance ingredient or is likely to change significantly;
- the 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(S)
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(S)
None.

NOTIFICATION IN OTHER COUNTRIES
Europe
South Korea (ECL) 2014
USA (TSCA) 2016

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Ambrocenide®

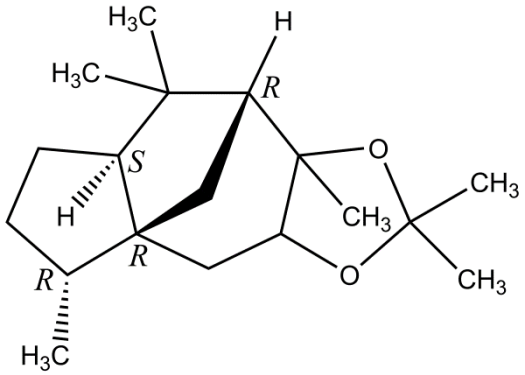
CAS NUMBER
211299-54-6

CHEMICAL NAME
4*H*-4a,9-Methanoazuleno[5,6-*d*]-1,3-dioxole, octahydro-2,2,5,8,8,9a-hexamethyl-, (4a*R*,5*R*,7a*S*,9*R*)-

OTHER NAMES
(4a*R*,5*R*,7a*S*,9*R*)-Octahydro-2,2,5,8,8,9a-hexamethyl-4*H*-4a,9-methanoazuleno[5,6-*d*]-1,3-dioxole
(1*R*,3*S*,7*R*,8*R*,10*R*,13*R*)-5,5,7,9,9,13-Hexamethyl-6,6-dioxatetrayclo(6.5.1.0(1,10).0(3,7)) tetradecane
CEDREN-AC
AMBROCENIDE® CRYST
F244

MOLECULAR FORMULA
$C_{18}H_{30}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
278.44 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 80%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	[3*R*-(3a,3ab,6a,7b,8aa)]-Hexahydro-3,6,8,8-tetramethyl-1*H*-3a,7-methanoazulen-5(4*H*)-one		
CAS No.	13794-73-5	*Weight %*	0.01–10
Hazardous Properties	Skin irritation (Category 2): H315 – Causes skin irritation		

Chemical Name	1*H*-3a,7-Methanoazulen-5-ol, octahydro-3,8,8-trimethyl-6-methylene-		
CAS No.	28231-03-0	*Weight %*	0.01–6
Hazardous Properties	Hazardous to the aquatic environment, long-term hazard (Category 2): H411 – Toxic to aquatic life with long lasting effects		

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name	6-(Methoxymethyl)-5,8 methano-1,4,4,trimethyl-1,2,3,3a,5,8-hexahydroazulene		
CAS No.	none	*Weight %*	0.01–2

Chemical Name	Cederen-15-ol		
CAS No.	none	*Weight %*	0.01–2

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white, crystalline solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	52.6–58.3 °C	Measured
Boiling Point	> 280.5 °C at 101.3 kPa	Measured
Density	1,094 kg/m^3 at 20.2 °C	Measured
Vapour Pressure	6×10^{-5} kPa at 20 °C	Measured
Water Solubility	4.28×10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	pH 4, $t_{½}$ = 42.8 days at 25 °C $t_{½}$ = 88.6 days at 20 °C pH 7 and 9, $t_{½}$ > 1 year at 25 °C	Measured
Partition Coefficient (n-octanol/water)	Log P_{OW} = 4.84 at pH 7 at 22 °C	Measured
Adsorption/Desorption	Log K_{OC} = 3.435	Calculated based on partition coefficient using KOCWIN v2.00 (US EPA, 2011)
Dissociation Constant	Not determined	Contains no dissociable functionalities
Particle Size*	D_{10}†: 107.9 µm D_{50}‡: 345.1 µm D_{90}‡: 670.7 µm	Measured.
Flash Point	150 °C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be flammable based on flash point
Autoignition Temperature	360 °C at 1,017 hPa	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 oxidative properties.

** Inhalable fraction (< 100 µm) given as 12.3% and respirable fraction (< 10 µm) given as 1.13%.*

† *D_{10} – average particle size where 10% of the particles have a smaller diameter.*

‡ *D_{50} – average particle size where 50% of the particles have a diameter smaller than the median.*

‡ *$D9_0$ - average particle size where 90% of the particles have a smaller 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 into Australia either in neat form for formulation into fragrance preparations and end-use products, as a component of fragrance preparation (at concentrations ≤ 40%) to be blended into end-use products, or as a component of end-use products (at concentrations ≤ 0.3%).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.2	0.4	0.6	0.7	0.8

PORT OF ENTRY
Sydney.

IDENTITY OF MANUFACTURER/RECIPIENTS
Symrise Australia Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as a component of a fragrance preparation (at concentrations ≤ 40%) in 25 kg plastic canisters or in lacquered drums of sizes ranging from 30 kg up to 200 kg and transported by road to the notifier's facility. The end-use products (containing the notified chemical at ≤ 0.3% concentration) will be packaged in containers suitable for retail sale.

When imported in its neat form, the notified chemical will be imported as a powder and packaged in 20 kg polyethylene/polyamide bags in cartons.

USE
The notified chemical will be used as a fragrance ingredient in a variety of cosmetic and household products (at proposed usage concentrations of ≤ 0.3% in fine fragrances, ≤ 0.02% in other cosmetic products and ≤ 0.01% in household products).

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging of the notified chemical will occur at the notifier's facility. Imported products containing the notified chemical (at concentrations ≤ 100%) will be stored at this facility until they are transported to customer facilities (in original importation packaging) or for reformulation into consumer products.

Reformulation
At the customer facilities, the notified chemical will be formulated into either a fragrance formula or end-use products. The reformulation procedure will likely vary depending on the nature of the formulated products, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and use closed systems with adequate ventilation, followed by automated filling of the reformulated products into containers of various sizes.

End-use
Household products
Household products containing the notified chemical (≤ 0.01% concentration) may be used by consumers and professional workers (such as cleaners). The products may be used in either closed systems or open manual processes including rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the household product will be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 0.3% 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	-	-
Blending, packaging and maintenance workers	4	2
Quality Control workers	0.5	2
Beauty care and Cleaning workers	1–8	200

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemical in its neat form, as a component of fragrance preparations (at concentrations ≤ 40%) or as a component of end-use products (at concentrations ≤ 0.3%) only in the event of accidental rupture of the drum containers.

At the notifier's facility, the primary work activity undertaken by transport and warehouse workers will include handling, loading and off-loading of drums or cartons containing the notified chemical at ≤ 100% concentration. Exposures of these workers will be limited to situations involving cleaning up from a spill or leaking drum. If such an event occurs, workers may mainly be exposed through dermal and ocular contact. Inhalation exposure to the notified chemical is not expected based on the low vapour pressure of the chemical at room temperature. The notifier states that such exposures will be minimised through the use of personal protective equipment (PPE) including protective coveralls, chemical resistant gloves and safety glasses.

Formulation of end products

During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during weighing and transfer stages, blending, quality control analysis, packaging of materials and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of adequate local ventilation and self-contained breathing apparatus if required, and through the use of PPE such as coveralls, goggles and impervious gloves.

Beauty care and cleaning professionals

Exposure to the notified chemical in end-use products (at ≤ 0.3% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use PPE to minimise repeated exposure, but the use is not always expected. However, the notifier states that good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the finished products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of a wide range of cosmetic and household products (at ≤ 0.3% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if the 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 (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, a dermal absorption (DA) of 100% was assumed for the notified chemical (ECHA, 2014). 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%, with the reminder ending up, as intended, on the hair. 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 (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.02	1	0.0244
Face cream	1,540	0.02	1	0.0048
Hand cream	2,160	0.02	1	0.0068
Fine fragrances	750	0.3	1	0.0352
Deodorant (non-spray)	1,500	0.02	1	0.0047
Shampoo	10,460	0.02	0.01	0.0003
Conditioner	3,920	0.02	0.01	0.0001
Shower gel	18,670	0.02	0.01	0.0006
Hand wash soap	20,000	0.02	0.01	0.0006
Hair styling products	4,000	0.02	0.1	0.0013
Total				**0.0788**

C = concentration of the 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	0.01	0.95	10	0.0003
Fabric softener	90	0.01	0.95	10	0.0001
Total					**0.0005**

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 Usage (g/cm^3)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.01	1,980	0.01	0.01	0.007	0.000003
Dishwashing liquid	3	0.01	1,980	0.009	0.01	0.03	0.000025
All-purpose cleaner	1	0.01	1,980	1	0.01	0.007	0.000217
Total							**0.000245**

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness on skin × Time Scale Factor × DA/ BW

Aerosol products (Inhalation exposure)

Product type	Amount (g/day)	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	0.02	20	1	20	50	1	10	0.0006

Daily systemic exposure = [(Amount × C × Inhalation Rate × Fraction Inhaled × 0.1) / BW × 1440)] × [Exposure Duration (Zone 1)/Volume (Zone 1) + Exposure Duration (Zone 2)/Volume (Zone 2)]

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 0.0801 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products may occur. However, it is considered that the combination of the conservative (screening level) 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 lower exposure factors (e.g., air fresheners).

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	irritating
Human, acute dermal irritation (10%)	non-irritating
Rabbit, eye irritation	irritating
Guinea pig, skin sensitisation – adjuvant test.	no evidence of sensitisation (at 75%)
Human, skin sensitisation – RIPT (0.05%)	no evidence of sensitisation
Human, skin sensitisation – RIPT (2.5%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL 200 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test in Chinese Hamster Ovary cells	non genotoxic

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemical were submitted.

Dermal absorption is expected to be limited given the low water solubility (4.28 mg/L) and high lipophilicity (log Kow = 4.84) of the notified chemical, limiting penetration of the hydrophilic epidermis. Given the low molecular weight (278.44 Da) of the notified chemical, absorption across the gastrointestinal and respiratory tract may occur.

Acute toxicity
The notified chemical is of low acute oral and dermal toxicity based on studies conducted in rats. In an acute dermal toxicity study, slight to well-defined erythema, scales and/or scabs were seen in four of five males, and all five female animals between days 2 and 11. Eight of the affected animals showed full recovery by Day 12, while the remaining affected animal (female) exhibited slight erythema throughout the observation period (15 days).

Irritation and sensitisation
The notified chemical is irritating to the skin based on a study conducted in rabbits. Very slight to slight erythema and oedema was observed in all animals at one hour after exposure, increasing in severity to slight to well-defined erythema over the 72 hour observation period. Desquamation was observed in 2/3 animals on day 7, and all animals on days 8 and 9. Two of the three animals had fully recovered 10 days after exposure, while the remaining animal continued to exhibit very-slight erythema and desquamation to the end of the observation period (day 12).

The notified chemical is irritating to the eye based on an acute study conducted on rabbits. Scattered or diffuse corneal opacity was recorded in all animals following exposure, persisting in one animal between 77 hours and 7 days. Slight iridial inflammation was observed on exposure with recovery within 24 hours. An increase in the severity of conjunctival redness from moderate to severe was observed following exposure with recovery indicated in 2/3 animals at the 77 hour observation, and in the remaining animal at the 7 day observation. Moderate to severe conjunctival swelling and slight to moderate conjunctival discharge was recorded in all animals following exposure with recovery in all animals at the 77 hour observation. All animals had fully recovered 14 days after exposure.

An acute dermal irritation study conducted on humans found that the notified chemical was non-irritating to humans at a concentration of 10%.

The notified chemical was not a skin sensitiser when tested in guinea pigs (at 75% concentration) or in two separate human repeated-insult patch studies (at 0.05% and 2.5% concentration).

Repeated dose toxicity
In a 28-day repeated dose oral gavage study (with two week recovery period) in rats the No Observed (Adverse) Effect Level (NO(A)EL) was established as 200 mg/kg bw/day based on clinical effects (hunched posture), a

decrease in thymus weight and vascular congestion in the kidneys in animals exposed to the highest dose tested (1,000 mg/kg bw/day).

Test substance related effects were also observed in the liver and stomach in both sexes. However, as animals exposed to the highest doses showed recovery from these effects during the recovery period the study authors considered these changes to be either a result of the irritating properties of the notified chemical (stomach) or an adaptive response (liver). Any other effects observed were considered to be non-adverse (or unrelated to exposure to the test substance) by the study authors as the effects were within the range of biological variation, could not be confirmed or did not show a dose-dependent relationship.

Mutagenicity/Genotoxicity
The notified chemical was non-mutagenic in a bacterial reverse mutation assay. In an *in vitro* mammalian chromosome aberration test in Chinese Hamster Ovary (CHO) cells, no statistically significant increases in the proportion of cells with chromosomal aberrations (including or excluding gap-type aberrations) were observed in the presence or absence of metabolic activation. A positive result was observed in one test where the frequency of gap-type aberrations was included in the analysis. Gaps are generally not included in the total aberration frequency and no statistically significant increase in the proportion of chromosomal aberrations was observed (in the presence or absence of metabolic activation) when the gaps were excluded from analysis. The positive result was not confirmed by the other tests, and so the notified chemical is not expected to be genotoxic.

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
Serious Eye Damage/Eye irritation (Category 2)	H319 – Causes serious eye irritation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Transport and Storage
Workers may experience dermal and accidental ocular exposure to the notified chemical (at ≤ 100% concentration) in the event of a discharge via spill or drum leakage. The use of PPE (e.g. impervious gloves, goggles, coveralls, hard hats and respiratory protection, if necessary) should minimise the potential for exposure. Provided adequate control measures and safe work practices are in place to minimise worker exposure, including PPE, the risk to workers from the notified chemical is not considered to be unreasonable.

Reformulation
Exposure of workers to the notified chemical (at ≤ 100% concentration) may occur during blending operations. The notified chemical is considered to be irritating to the skin and eyes. In addition, harmful effects following inhalation and/or repeated exposure to the notified chemical are possible. Therefore, caution should be exercised when handling the notified chemical during reformulation processes.

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

End-use
Cleaners and beauty care professionals will handle the notified chemical at up to 0.3% concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experience by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health

Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products (containing the notified chemical at ≤ 0.3% in individual products). The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Irritation

The notified chemical was irritating to the skin and eyes. However, given the low proposed use concentration (≤ 0.3%) and the absence of irritation effects on human skin at a concentration of 10%, irritation effects are not expected.

Repeat dose toxicity

The potential systemic exposure to the public from the use of the notified chemical in cosmetics and household products was estimated to be 0.0801 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 200 mg/kg bw/day, which was derived from a 28 day repeated dose oral gavage toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 2,496. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Based on the potential systemic exposure from the notified chemical in cosmetics and household products, an MOE value greater than or equal to 100 is also expected where the notified chemical is present at ≤ 0.8% concentration.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.3% in fine fragrances, ≤ 0.0.2% in other cosmetics and ≤ 0.01% in 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 neat or as a component of fragrance formulations, for reformulation into finished cosmetic formulations and household 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 adsorbents, 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. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail and end-use. Wastes containing the notified chemical generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. It is estimated by the notifier that up to 1% of the import volume of the notified chemical (or up to 8 kg) may be released from reformulation processes. These will be collected and released to on-site waste water treatment processes, or released to sewers in a worst case scenario. Empty import containers are expected to be recycled or disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic formulations and household products.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the notified chemical may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical will be released to sewer after use. Based on its low water solubility (4.28 mg/L) and high calculated adsorption coefficient (log K_{OC} = 3.435), most of the notified chemical released to sewer is expected to be

removed at sewage treatment process by partitioning to sludge or sediment. Limited amount of the notified chemical remaining in effluent from sewage treatment plants may enter to surface waters.

Based on the results of two ready biodegradability studies, the notified chemical is not considered readily biodegradable (0% and 8.36% in 28 days). For details of the environmental fate studies, please refer to Appendix C.

The notified chemical has the potential to be bioaccumulative based on its high partition coefficient (log K_{OW} = 4.84), small molecular size and lack of ready biodegradability. However, the notified chemical is not expected to be significantly released to surface waters and is not harmful to aquatic life up to the limit of its water solubility.

The notified chemical in water, landfill, soil, and sludge is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	800	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	800	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.19	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	Million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.485	µg/L
PEC - Ocean:	0.049	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). Using these assumptions, irrigation with a concentration of 0.49 µg/L may potentially result in a soil concentration of approximately 3.23 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 16.15 µg/kg and 32.31 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from an ecotoxicological investigation conducted on the notified chemical are summarised in the table below. Details of this study can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 > 2.77 mg/L	Not harmful to fish up to water solubility limit
Daphnia Toxicity	48 h EC50 > 3.12 mg/L	Not harmful to aquatic invertebrates up to water solubility limit
Algal Toxicity	72 h EC50 > 4.58 mg/L	Not harmful to algae up to water solubility limit
Inhibition of Bacterial Respiration	3 h IC50 > 4.3 mg/L	Not inhibitory to microbial respiration up to water solubility limit

Based on the above ecotoxicological endpoint for the notified chemical, it is not expected to be harmful to aquatic life up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the Globally

Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the available endpoint for fish. A safety factor of 100 was used given acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	> 2.77	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	> 27.7	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	0.485	> 27.7	**< 0.017**
Q – Ocean	0.049	> 27.7	**< 0.002**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. Although the notified chemical is not readily biodegradable and has the potential for bioaccumulation, it is not expected to be harmful to aquatic life up to the limit of its water solubility. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 52.6–58.3 °C

Method OECD TG 102 Melting Point/Melting Range.
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks Capillary method. Purity of test substance 96.6%.
Test Facility GAB & IFU (1998a)

Boiling Point > 280.5 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Remarks Siwoloboff method. Purity of test substance 96.6%. No boiling was observed up to the limit of heating of the substance.
Test Facility GAB & IFU (1998b)

Density 1,094 kg/m^3 at 20.2 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Air comparison pycnometer method. Purity of test substance ≥ 81%
Test Facility GAB & IFU (1998c)

Vapour Pressure 6×10^{-5} kPa at 20 °C

Method OECD TG 104 Vapour Pressure.
Remarks Static technique. Purity of test substance 96.6%.
Test Facility NOTOX (1998a)

Water Solubility 4.28×10^{-3} g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 92/69 A.6 Water Solubility.
Remarks Column Elution Method
Test Facility GAB & IFU (1998d)

Hydrolysis as a Function of pH $t_{½}$ = 42.8 days at pH 4 at 25 °C
$t_{½}$ = 88.6 days at pH 4 at 20 °C
$t_{½}$ > 1 year at pH 7 and 9 at 25 °C

Method OECD TG 111 Hydrolysis as a Function of pH.
EC Council Regulation No 92/69 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	$t_{½}$
4	25	42.8 days
7	25	> 1 year
9	25	> 1 year

Remarks After 5 days under the accelerated conditions of 50 °C the rate of hydrolysis of the test substance was less than 10% at pH 7 and 9. This equates to a half-life at 25 °C of $t_{½}$ > 1 year. At pH 4, the half-life of the test substance was determined to be 36.6–40.1 hours under accelerated conditions of 50 °C. This equates to a half-life at 25 °C of $t_{½}$ = 42.8 days. Therefore, under the conditions of the test, the test substance is expected to be hydrolytically stable under neutral and basic conditions. The test substance is expected to hydrolyse slowly under acidic conditions.
Test Facility GAB & IFU (1998e)

Partition Coefficient (n-octanol/water) log Pow = 4.84 at pH 7 at 22 °C

Method OECD TG 107 Partition Coefficient (n-octanol/water).
EC Council Regulation No 92/69 A.8 Partition Coefficient.
Remarks Shake Flask Method
Test Facility GAB & IFU (1998g)

Particle Size D_{50} = 345 µm

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

Average particle diameter (µm)	*Mass (%)*
< 107.9	10
< 345.1	50
< 670.7	90

Remarks Laser diffraction method. Purity of test substance 99.6%.
Particle size distribution provided for two tests. All particle sizes greater than 3.753 µm.
Test Facility consilab (2015)

Flash Point 150 °C at 101.3 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks Untranslated study report provided in German.
Test Facility Bayer (2014)

Autoignition Temperature 360 °C at 101.7 kPa

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks Untranslated study report provided in German.
Test Facility Bayer (2014)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 401 Acute Oral Toxicity.
Species/Strain	Rat/Hsd/Cpb:WU
Vehicle	Peanut oil
Remarks - Method	No significant protocol variations. GLP certificate.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	2 F	2,000	0/2
2	5 M, 3 F	2,000	0/8

LD50	> 2,000 mg/kg bw
Signs of Toxicity	None.
Effects in Organs	None.
Remarks - Results	No mortalities. No abnormal clinical findings.
CONCLUSION	The notified chemical is of low toxicity via the oral route. All animals made the expected gains in bodyweight.
TEST FACILITY	medcon (1997a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity.
Species/Strain	Rat/Wistar/Crl:(WI) BR
Vehicle	Propylene glycol
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP certificate. Test substance administered as supplied (purity ≥ 81%).

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Slight to well-defined erythema, scales and/or scabs were seen in the treated skin-area in 4/5 male and 5/5 female animals between days 2 and 11. All affected animals except one showed full recovery by Day 12. The remaining affected animal (female) exhibited slight erythema throughout the observation period (15 days).
Signs of Toxicity - Systemic	Lethargy was recorded in one male on day 1 (4 hours after exposure) and red staining of the left eye (periorbital region) was recorded in another male (1/5) on day 2. No other clinical signs were recorded.
Effects in Organs	None.
Remarks - Results	There were no mortalities observed. All animals made the expected body weight gains

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

TEST FACILITY NOTOX (1998b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 3
- Vehicle: Peanut oil.
- Observation Period: 12 days
- Type of Dressing: Semi-occlusive.
- Remarks - Method: No significant protocol variations.
  GLP certificate.
  Test substance administered as supplied (purity ≥ 81%).
  Sex of the animals was not provided.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2.7	3	3	3	> 12 days	1
Oedema	2.3	2	2.7	3	< 8 days	0

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

Remarks - Results: Very slight to slight erythema and oedema was observed in all animals at one hour after exposure, increasing in severity (slight to well-defined erythema) at the 24, 48 and 72 hour observation periods. Recovery indicated on day 4 in 2/3 animals, with 1/3 animals exhibiting very-slight erythema on day 12 (no oedema observed from day 8).

Desquamation was observed in 2/3 animals on day 7, and all animals on days 8 and 9. Desquamation persisted in one animal to the end of the observation period (days 10–12).

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY medcon (1997b)

B.4. Skin irritation – human volunteers

TEST SUBSTANCE Notified chemical (10%)

METHOD
- Study Design: 48 hour patch test
  Patch containing 0.2 mL test substance was applied to upper back for 48 hours.
- Study Group: 46 F, 7 M; age range 19–78 years
- Vehicle: DEP/EtOH 3:1
- Remarks - Method: No GLP certificate.
  Occluded. The test substance was spread on a 1.9 cm × 1.9 cm patch.

RESULTS
- Remarks - Results: 53/53 subjects completed the study.

  No visible skin reactions were observed.

CONCLUSION The notified chemical (at 10% concentration) was non-irritating under the conditions of the test.

TEST FACILITY CPT (2006)

B.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3 M
Observation Period 14 days
Remarks - Method No significant protocol variations (72 h observation was made at 77 h).
GLP certificate.
Test substance administered as supplied (purity ≥ 81%).

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	1.7	3	2	3	< 14 days	0
Conjunctiva: chemosis	0.3	1	1	2	< 77 hours	0
Conjunctiva: discharge	0.3	1	0.7	1	< 77 hours	0
Corneal opacity	0	1	0.3	1	< 7 days	0
Iridial inflammation	0	0	0	0	-	0

* Calculated on the basis of the scores at 24, 48, and 77 hours for EACH animal.

Remarks - Results Scattered or diffuse corneal opacity was recorded in all animals following exposure, persisting in one animal between 77 hours and 7 days. Slight iridial inflammation was recorded following exposure but was absent at the 24 hour observation.

Moderate conjunctival redness increasing in severity was observed following exposure. Recovery was indicated in 2/3 animals at the 77 hour observation, and in the remaining animal at the 7 day observation. Moderate to severe conjunctival swelling and slight to moderate conjunctival discharge was recorded in all animals following exposure with recovery in all animals at the 77 hour observation.

The treated eyes showed no eye irritation effects after 14 days.

CONCLUSION The notified chemical is irritating to the eye.

TEST FACILITY NOTOX (1998c)

B.6. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – adjuvant test
Species/Strain Guinea pig/Pirbright white/Hsd/Poc:DH
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 1%
topical: 75%
MAIN STUDY
Number of Animals Test Group: 10 M, 10 F Control Group: 10
Vehicle Peanut oil

Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 4-Aminobenzoic acid ethyl ester.
INDUCTION PHASE	Induction Concentration: intradermal: 1% topical: 100%
Signs of Irritation	Following the intradermal and topical induction phases, slight irritation was observed. In order to induce mild inflammation, the test area was re-clipped and pre-treated with 10% sodium lauryl sulfate in Vaseline 24 hours prior to repeat exposure to the test substance.
CHALLENGE PHASE	
1st challenge	topical: 75% (occlusive dressing)
Remarks - Method	No significant protocol variations GLP certificate. Test substance supplied at ≥ 81% purity.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	75%	0/20	0/20
Control Group	75%	0/10	0/10

CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	medcon (1997c)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (0.05%)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded 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 by the applicants after 24 h. Sites were graded 24 and 72 h after application.
Study Group	88 F, 27 M; age range 16–79 years
Vehicle	DEP/EtOH 3:1
Remarks - Method	No GLP certificate. Occluded. The test substance was spread on a 1.9 cm × 1.9 cm patch and allowed to volatise for a minimum of 15–40 minutes before being applied to test subjects.
RESULTS	
Remarks - Results	105/115 subjects completed the study. Three subjects withdrew prior to commencing the test, 2 subjects withdrew following one induction reading, 1 subject withdrew following 3 induction readings, 1 subject withdrew following 4 induction readings, 1 subject withdrew following 7 induction readings, and 2 subjects failed to attend for the challenge phase. All subjects withdrew voluntarily, and for reasons unrelated to application of the test substance.

	No visible skin reactions were observed during the induction or challenge phases in any of test subjects.
CONCLUSION	The notified chemical (at 0.05% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	CPT (2007)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (2.5%)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded 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 by the applicants after 24 h. Sites were graded 24 and 72 h after application.
Study Group	81 F, 33 M; age range 16–78 years
Vehicle	DEP/EtOH 3:1
Remarks - Method	No GLP certificate. Occluded. The test substance was spread on a 1.9 cm × 1.9 cm patch and allowed to volatise for 40 minutes before being applied to test subjects.
RESULTS	
Remarks - Results	105/114 subjects completed the study. Five subjects withdrew prior to commencing the test, 2 subjects withdrew following 5 induction readings, 1 subject withdrew following 1 induction reading and 1 subject withdrew following 4 induction readings. All subjects withdrew voluntarily, and for reasons unrelated to application of the test substance. Two subjects did not present for the first reading following supervised removal of the patch (prior to induction phase). Barely perceptible erythema was observed in 1 subject at induction readings 1 and 2. No other visible reaction was observed over the remainder of the induction and challenge phases. One subject exhibited mild to moderate erythema and oedema at induction readings 4 and 5 respectively. The patch was moved following induction reading 5, and barely perceptible erythema was recorded at induction reading 6. No other visible reactions were observed during the induction or challenge phases. The remaining test subjects exhibited no visible skin reactions during the induction or challenge phases in any of test subjects.
CONCLUSION	The notified chemical (at 2.5% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	CPT (2008)

B.9. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Wistar Crl:(WI) BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days

	Dose regimen: 7 days per week Post-exposure observation period: 15 days
Vehicle	Propylene glycol
Remarks - Method	No significant protocol variations GLP certificate. Test substance supplied at ≥ 81% purity.

RESULTS

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

Mortality and Time to Death

One female in the high-dose group was found dead on day 19. No cause of death could be established and no corroborative findings in other animals were observed and the death was considered by the study authors to be accidental. No other unscheduled deaths were recorded.

Clinical Observations

Hunched posture was observed in females in the high-, high-dose recovery (4/5 and 5/5 respectively) and control (1/5) groups with recovery indicated during the non-exposure (recovery) period. Hunched posture and piloerection was observed in the female animal that died (high-dose group). Excessive salivation was observed in all males exposed to the test substance (compared to 2/10 in the control groups), and in all females in the mid- and high-dose exposure groups (compared to 1/5 in the low-dose group and 2/10 in the control groups). Rales were recorded in control and exposed animals (1/5 female, control-recovery group; 1/5 male high dose group). The study authors considered the effects to be related to multiple intra-oesophageal intubation and/or the taste of the test substance rather than signs of systemic toxicity.

Observations of excessive alopecia (all males in the low-dose group), mild alopecia, red or brown staining of the skin, the presence of scabs or scales on the skin, abnormal foreleg posture, eye injury and extremely increased motor activity (1/5 control, 2/5 control-recovery group females, and one female in the high-dose recovery group) or abnormalities in ophthalmology (one male in each of the low- and high-dose recovery groups and one female in the control recovery group) were not considered to be toxicologically significant or related to exposure to the test substance by the study authors as the effect was either present prior to exposure, within the range of biological variation, did not show a dose-dependent relationship, could not be corroborated or was a result of group environment or sampling trauma.

All animals made the expected body weight gains over the course of the exposure and recovery periods.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

A small statistically significant difference in prothrombin time and platelet count was observed after 4 weeks in animals in the high-dose group. The study authors did not consider this to be biologically relevant as the values observed were within the range of historical background data and the statistical significance may have been due to low values in the control group. No other treatment related effects were recorded.

Differences between the clinical biochemistry of animals exposed to the test substance compared to those in the control groups were observed, including: a decrease in aminotransferase activity in males exposed to mid- and high-doses (levels recovered during the non-exposure period) changes in inorganic phosphate, calcium and glucose levels (during and after exposure to the mid- and high-doses of test substance in males and/or females) and high levels of triglycerides in females exposed to the highest dose (levels recovered during the non-exposure period). These differences were not considered to be of biological relevance or as a result of exposure to the test substance by the study authors, as observed values were within the range of historical background data or showed no dose-response relationship.

Effects in Organs

A thickening or irregular surface of the forestomach and/or limiting ridge [all males, mid- and high-dose groups; some females (1/5 and 3/4 in the mid- and high-dose groups respectively)] was accompanied by minimal to moderate squamous hyperplasia. Following the recovery period, only slight to minimal squamous hyperplasia was observed in 1/5 males and 1/5 females (respectively). A dark-red discoloration and simple vascular congestion of the kidney medulla was observed (1/5 males in the low-dose group and 5/5 males and 1/4 females in the high-dose group) without corresponding morphological alterations. Within the liver, a red-brown discolouration and/or accentuated lobular pattern in the liver (5/5 males and 3/4 females in the high-dose group) were observed. Midzonal/centrilobular hypertrophy was observed in 1/5 males in the mid-dose group (minimal), 5/5 males in the high-dose group (slight to moderate) and 3/4 females in the high-dose group (minimal to slight). A slight degree of bile duct pigment was also observed in 1/5 males in the high-dose group.

Recovery was indicated by the absence of these effects in animals in the high-dose recovery groups. Any other changes were not considered to be related to the test substance by the study authors, but within the range of biological variation.

Males and females exposed to the highest dose exhibited statistically significant increases in absolute and/or relative liver weights at the end of the exposure and recovery periods. Other changes included a decrease in the weight of the thymus (males in the high-dose group) and a statistically significant increase in relative heart weight (males in the mid-dose group) were not considered a sign of toxicity by the study authors as the effect was not observed in females, and a dose-response relationship was not observed.

Remarks – Results

Effects in the liver and stomach were observed in animals exposed to the middle and highest doses of the test substance. The study authors attributed the effects on the stomach to the irritating properties of the test substance and recovery was indicated with only slight to moderate squamous hyperplasia observed in 2/10 animals (one male and one female) previously exposed to the highest dose. Liver effects including macroscopic and microscopic changes as well as a statistically significant increase in relative liver weight were predominantly observed in animals exposed to the highest dose with microscopic effects observed in one male in the mid-dose group. While recovery from the macroscopic and microscopic effects of the test substance was indicated the relative liver weight of males and females at the end of the recovery period remained significantly higher than those of the animals in the control group.

Vascular congestion in the kidneys and a decrease in thymus weight were observed in all males in the high-dose group.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 200 mg/kg bw/day in this study, based on the effects on the thymus and kidneys in males.

TEST FACILITY	NOTOX (1998d)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100
Metabolic Activation System	S9 fraction from Aroclor induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 0–1,000 µg/plate b) Without metabolic activation: 0–1,000 µg/plate
Vehicle	Ethanol
Remarks - Method	No significant protocol variations GLP certificate. Test substance supplied at ≥ 81% purity. Positive controls: without metabolic activation – sodium azide (TA100, TA1535), 2-nitrofluorene (TA98) and 9-aminoacridine (TA1537); with metabolic activation – 2-aminoanthracene.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 625	> 1,000	> 1,000	none
Test 2		> 1,000	> 1,000	none
Present				
Test 1		> 1,000	> 1,000	none
Test 2		> 1,000	> 1,000	none

Remarks - Results

Precipitation of the test substance was noted at 1,250, 2,500 and 5,000 µg/plate. A reduction in the bacterial lawn was noted at 78.12 and 156.25 µg/plate with complete absence at higher concentrations. Cytotoxicity was noted at 625 µg/plate where the number of revertants present was reduced to 48% of those not exposed to the test substance.

No significant increase in the numbers of revertants, in the presence or absence of metabolic activation was observed in any of the strains tested.

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

Labor (1998a)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Chinese Hamster/ K1-BH(4)
Cell Type/Cell Line: Fibroblasts/CHO-cell line
Metabolic Activation System: S9 fraction from phenobarbital/β-Naphthoflavone induced rat liver.
Vehicle: Ethanol
Remarks - Method: No significant protocol variations
GLP certificate.
Test substance supplied at ≥ 81% purity.
Positive controls: without metabolic activation – methylmethanesulphonate; with metabolic activation – cyclophosphamide.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time (h)*
Absent			
Test 1A	2.5, 5.0, 10.0, 20.0*, 30.0*, 40.0*	24	18 h
Test 1B	2.5, 5.0, 10.0, 20.0*, 30.0*, 40.0*		28 h
Test 2A	3.12, 6.25, 12.5*, 25.0*, 50.0*		18 h
Test 2B	3.12, 6.25, 12.5, 25.0, 50.0*		28 h
Present			
Test 1A	6.25*, 12.5*, 25.0, 50.0, 100.0*	3	18 h
Test 1B	6.25*, 12.5*, 25.0, 50.0, 100.0*		28 h
Test 2A	7.5, 15.0, 30.0*, 60.0*, 90.0 120.0*		18 h
Test 2B	7.5, 15.0, 30.0, 60.0, 90.0 120.0*		28 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 1A	≥ 31.25 µg/mL	≥ 40 µg/mL	> 40.0 µg/mL	negative
Test 1B		> 40 µg/mL	> 40.0 µg/mL	negative
Test 2A		≥ 50.0 µg/mL	> 50.0 µg/mL	negative
Test 2B		≥ 50.0 µg/mL	> 50.0 µg/mL	negative
Present				
Test 1A	≥ 31.25 µg/mL	> 100 µg/mL	> 100.0 µg/mL	negative
Test 1B		≥ 100 µg/mL	> 100.0 µg/mL	positive
Test 2A		> 120 µg/mL	> 120.0 µg/mL	negative
Test 2B		> 120 µg/mL	> 120.0 µg/mL	negative

Remarks - Results

In Test 1A, 2A and 2B, no statistically significant increases in the proportion of cells with chromosomal aberrations (including or excluding gap-type aberrations) were observed in the presence or absence of metabolic activation.

In Test 1B, a statistically significant increase in the proportion of cells with chromosomal aberrations (in the presence of metabolic activation) was observed when gap-type aberrations were included. Gaps are generally not included in the total aberration frequency, and when gaps were excluded, no statistically significant increase in the proportion of chromosomal aberrations was observed in the presence or absence of metabolic activation. This result was not confirmed by Test 2B.

No polyploid metaphases were observed.

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

Labor (1998b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Toxicity control*		*Sodium benzoate*	
Day	*% Degradation*	*Days*	*% Degradation*	*Day*	*% Degradation*
7	0	7	16.1	7	56.9
14	0	14	17.4	14	65.9
21	0	21	26.8	21	91.8
28	0	28	26.8	28	99.8

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound attained the threshold level of 60% by 8 days. Therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 21 days (26.8%; 26.8% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 0%. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 D) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	GAB& IFU (1997)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	BOD Test for Insoluble Substances (BODIS)
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	1.62	7	79.46
14	6.97	14	86.16
21	7.34	21	88.30
28	8.36	28	89.63

Remarks – Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 7 days (79.46%). Therefore, the tests indicate the suitability of the inoculum. The degree of degradation of the test substance after 28 days was 8.36%. Therefore, the test substance is not considered to be readily biodegradable according to the BODIS guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	GAB (1997)

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.
Species	*Oncorhynchus mykiss* (rainbow trout)
Exposure Period	96 hours
Auxiliary Solvent	Acetone
Water Hardness	148 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography (GC)
Remarks – Method	The test substance was dissolved in acetone due to its low solubility in water. This was followed by diluting the solution in test medium. The definitive test was conducted at the nominal loading rates of 0.43, 2.13 and 4.26 mg/L of the test substance, which correspond to average effective concentrations of 0.28, 1.38 and 2.77 mg/L of the test substance. The highest nominal concentration tested (4.26 mg/L) was determined to be the saturation concentration of the test substance in the stock solution. The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0
0.43	0.28	10	0	0	0	0	0
2.13	1.38	10	0	0	0	0	0
4.26	2.77	10	0	0	0	0	0

LC50	> 2.77 mg/L at 96 hours
NOEC	0.28 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the test period. The actual concentration of the test substance was measured every 24 hour. The 96 h LC50 and NOEC for fish were determined to be > 2.77 mg/L and 0.28 mg/L, respectively, based on the measured average effective concentrations.
CONCLUSION	The notified chemical is not considered to be harmful to fish up to the limit of its solubility in water.
TEST FACILITY	GAB & IFU (1998g)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction

	Test – Semi-static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone
Water Hardness	103.53 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test substance was dissolved in acetone due to its low solubility in water. This was followed by diluting the solution in test medium. The definitive test was conducted at the nominal loading rates of 2.4 and 4.8 mg/L of the test substance, which correspond to average effective concentrations of 1.56 and 3.25 mg/L of the test substance. The highest nominal concentration tested (4.8 mg/L) was determined to be the saturation concentration of the test substance in the stock solution. The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
2.4	1.56	20	0	0
4.8	3.12	20	0	0

EC50	> 3.12 mg/L at 48 hours
NOEC	1.56 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the test period. The actual concentrations of the test substance were measured every 24 hours during the 48 h test period. The 48 h EC50 and NOEC for daphnids were determined to be > 3.25 mg/L and 1.56 mg/L, respectively, based on the measured average effective concentrations.

CONCLUSION The notified chemical is not considered to be harmful to aquatic invertebrates up to the limit of its solubility in water.

TEST FACILITY GAB & IFU (1998h)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test.
Species	*Scenedesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 4.3 mg/L Actual: 4.58 mg/L
Auxiliary Solvent	Acetone
Water Hardness	Not reported
Analytical Monitoring	GC
Remarks - Method	The test substance was dissolved in acetone due to its low solubility in water. This was followed by diluting the solution in test medium. As no effects were observed at the highest concentration tested in the range finding test (conducted at the nominal concentrations of 0.01, 0.1, 1.0, and 4.3 mg/L), the definitive test was conducted at a single nominal loading rate of 4.3 mg/L of the test substance. This nominal concentration (4.3 mg/L) was determined to be the saturation concentration of the test substance in the stock solution. The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 48 h	*mg/L*	*mg/L at 48 h*	*mg/L*
> 4.58	4.58	> 4.58	4.58

Remarks - Results: All validity criteria for the test were satisfied. The actual concentrations of the test substance were measured every 24 hours during the test period. The 48 h EC50 and NOEC for algae were determined to be > 4.58 mg/L and 4.58 mg/L, respectively, based on the measured average effective concentrations.

CONCLUSION: The notified chemical is not considered to be harmful to algae up to the limit of its solubility in water.

TEST FACILITY: GAB & IFU (1998i)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 209 Activated Sludge, Respiration Inhibition Test.
- Inoculum: Activated sewage sludge
- Exposure Period: 3 hours
- Concentration Range: Nominal: 4.3 mg/L; Actual: Not determined
- Remarks – Method: The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. The test substance was dissolved in acetone due to its low solubility in water. This was followed by diluting the solution in test medium. 3,5-Dichlorophenol was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 30 minutes and 3 hours of exposure.

RESULTS
- IC50: > 4.3 mg/L at 3 hours
- NOEC: Not determined
- Remarks – Results: All validity criteria for the test were satisfied. The 3 h IC50 was determined to be > 4.3 mg/L, based on the nominal concentration.

CONCLUSION: The notified chemical is not inhibitory to microbial respiration up to the limit of its solubility in water.

TEST FACILITY: GAB & IFU (1998j)

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