File No: STD/1639

April 2018

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexane, 1,4-bis(ethoxymethyl)-

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
STD/1639	BASF Australia Ltd	Cyclohexane, 1,4-bis(ethoxymethyl)-	Yes	< 2 tonnes per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical 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

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 Aquatic Toxicity (Category 3)	H402 – Harmful to aquatic life
Chronic Aquatic Toxicity (Category 3)	H412 – Harmful to aquatic life with long lasting effects

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

  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
  - Good general ventilation, including local exhaust ventilation if possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the 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 containment, physical 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 concentration of the two notified chemical exceeds or is intended to exceed 0.2% 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 product containing 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)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12, 28 Freshwater Place
SOUTHBANK VIC 3006

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year)

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: analytical data, degree of purity, impurities, use details, import volume, and site of manufacture/reformulation.

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, Dissociation Constant, Genotoxic in vivo, Repeated Dose Toxicity, and Bioaccumulation.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China, Europe, Switzerland, Taiwan and USA

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Vertofruct®

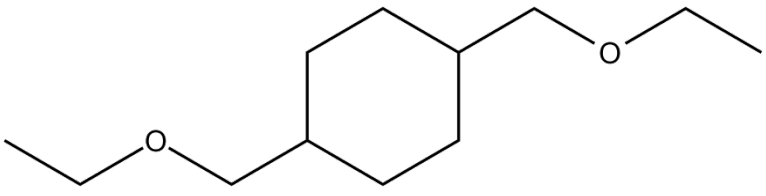
CAS NUMBER
54889-63-3

CHEMICAL NAME
Cyclohexane, 1,4-bis(ethoxymethyl)-

OTHER NAME(S)
1,4-Bis(ethoxymethyl)-cyclohexane

MOLECULAR FORMULA
$C_{12}H_{24}O_2$

STRUCTURAL FORMULA



The notified chemical consists of a mixture of trans and cis isomers.

MOLECULAR WEIGHT
200.3 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear, colourless liquid with fruity odour

Property	Value	Data Source/Justification
Melting Point/Freezing Point	10 °C	Measured
Boiling Point	244.9 °C at 101.3 kPa	Measured
Density	899 kg/m^3 at 20 °C	Measured
Vapour Pressure	1×10^{-3} kPa at 20 °C	Measured
Water Solubility	0.57 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemicals are unlikely to hydrolyse significantly in the environment pH of 4-9.
Partition Coefficient (n-octanol/water)	log Pow = ~ 3 at 23 °C	Due to surface active properties, the Pow is estimated
Adsorption/Desorption	log Koc = 2.44 at 23 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Surface Tension	51 mN/m at 20 °C	Measured
Flash Point	105.5 °C	Measured
Flammability	Not highly flammable	Measured
Autoignition Temperature	185 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that imply oxidising properties

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for 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. It will be imported into Australia in neat form for reformulation or in finished end-use products at < 0.2% concentrations.

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

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

PORT OF ENTRY
Throughout Australia

TRANSPORTATION AND PACKAGING

The notified chemical will be imported into Australia in neat form in sealed steel drums or as a component of finished consumer products in standard consumer packaging. The imported finished and reformulated consumer products will be transported by road to retail stores for distribution.

USE

The notified chemical will be imported as a fragrance ingredient for use in perfumes, cosmetic and household products. The proposed final concentration of the notified chemical in end-use products will be < 0.2%.

OPERATION DESCRIPTION

Reformulation

The procedures for incorporating the notified chemical into end-use products 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 for the reformulation process, the notified chemical will be weighed and added to the mixing vessel where they will be blended with additional additives to form the finished cosmetic and household products. The blending operations are expected to be in closed systems and highly automated with adequate ventilation. This will be followed by automated filling of the reformulated products into containers of various sizes. During the reformation process, samples of the notified chemical and the finished products will be taken for quality control testing. Cleaning and maintenance of the equipment process is also expected at the end of the reformulation operation.

End use

Cosmetic products

The finished cosmetic products containing the notified chemical at < 0.2% concentrations will be used by consumers and professionals such as beauticians and hairdressers. Depending on the nature of the products, applications may be by hand, spray or through the use of applicators.

Household products

Household products containing the notified chemical at < 0.2% concentrations 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 followed by wiping. In some cases the household product may be diluted with water prior to application.

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 exposure only
Plant operator - mixer	4	10 – 20
Plant operator – drum handling	4	10 – 20
Plant operator – drum cleaning/washing	4	10 – 20
Maintenance	4	10 – 20
Quality control	0.5	10 – 20
Professional end users	8	240

EXPOSURE DETAILS

Transport and Storage

Transport and warehouse workers may come into contact with the notified chemical at ≤ 100% concentration when handling the imported neat chemical, fragrance formulations and/or end-use products in the event of a spill or rupture of containers. Incidental exposure to the notified chemical may occur via the skin or eye during the clean-up of accidental spills. Exposure will be minimised through the use of personal protective equipment (PPE) including impervious gloves, coveralls, hard hats and safety glasses.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers may occur during weighing and transfer stages, blending, quality control analysis, packaging and cleaning and maintenance of equipment. The notifier stated that reformulation sites are expected to implement control measures for workers such as enclosed systems with local exhaust ventilation and use of PPE such as coveralls, impervious gloves, goggles and respiratory protection if required.

End-use by professionals
Exposure to the notified chemical in end-use products (at < 0.2% 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 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 the cosmetic and household products with < 0.2% concentrations of the notified chemical. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of various types of cosmetic and household cleaning product categories (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006) in which the notified chemical may be used are shown in the following tables. For the purposes of exposure assessment via the dermal route, Australian use patterns for various products are assumed to be similar to the consumer use patterns in Europe. In the absence of dermal absorption data and based on the low molecular weight of the notified chemical (200.3 g/mol), a dermal absorption (DA) of 100% was assumed (ECHA, 2017). For inhalation exposure estimation of spray products, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009) with an adult inhalation rate of 20 m^3/day (enHealth, 2012). It was conservatively assumed that the fraction of the notified chemical inhaled will be 50%, with the remainder ending up on the targets as intended. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was applied in the calculations.

Cosmetic products (dermal exposure)

Product type	*Amount (mg/day)*	*Chemical concentration (%)*	*Retention Factor (RF)*	*Daily systemic exposure (mg/kg bw/day)*
Body lotion	7820	0.2	1.000	0.2444
Face cream	1540	0.2	1.000	0.0481
Hand cream	2160	0.2	1.000	0.0675
Fine fragrances	750	0.2	1.000	0.0234
Deodorant (non-spray)	1500	0.2	1.000	0.0469
Shampoo	10460	0.2	0.010	0.0033
Conditioner	3920	0.2	0.010	0.0012
Shower gel	18670	0.2	0.010	0.0058
Hand wash soap	20000	0.2	0.010	0.0063
Hair styling products	4000	0.2	0.100	0.0125
Total				**0.4594**

Daily systemic exposure = (Amount × Chemical concentration × RF × DA)/BW
(RF = retention factor; DA = dermal absorption; BW = body weight)

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	*Amount (g/use)*	*C (%)*	*Product Retained (%)*	*Product Transferred (%)*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	230	0.2	0.95	10	0.0068
Fabric softener	90	0.2	0.95	10	0.0027
Total					**0.0095**

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW
(C = chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

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*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	1.43	0.2	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.2	1980	0.009	0.01	0.03	0.0005
All-purpose cleaner	1	0.2	1980	1	0.01	0.007	0.0043
Total							**0.0049**

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

(C = chemical concentration; DA = dermal absorption; BW = body weight)

Aerosol products (Inhalation exposure)

Product type	*Amount (g/day)*	*C (%)*	*Exposure Duration (Zone 1) (min)*	*Exposure Duration (Zone 2) (min)*	*Volume (Zone 1) (m3)*	*Volume (Zone 2) (m3)*	*Daily systemic exposure (mg/kg bw/day)*
Hairspray	*9.89*	*0.2*	*1*	*20*	*1*	*10*	***0.0064***

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 1 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

Note - conversion factors of 0.1 [to account for C/Bioavailability as a % and unit conversion (g to mg) ((1/100 × 1/100) × 1000)]

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 0.4802 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 (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 and deodorants).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5.2 mg/L/4 hour; low toxicity
Skin irritation (*in vitro*)	irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral/gavage toxicity – 28 days. (no vehicle)	NOAEL = 50 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* HPRT	non genotoxic
Genotoxicity – *in vitro* Micronucleus in V79 cells	non genotoxic
Rat, reproductive and developmental toxicity (chemical in corn oil)	NOAEL = 50 mg/kg bw/day

Toxicokinetics, metabolism and distribution

No toxicokinetic data on the notified chemical was submitted.

Given the low molecular weight (200.3 g/mol) of the notified chemical and the log Pow of 3, absorption across biological membranes may occur.

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

Irritation and sensitisation
The notified chemical is irritating to the skin based on the results of in vitro skin irritation study conducted using a reconstructed human epidermis model. On the basis of the study, the notified chemical is considered to skin irritant (Cat 2) according to the GHS criteria.

Based on the results of an eye irritation study in rabbits, the notified chemical is slightly irritating to the eyes and is not to be classified according to the GHS criteria.

No information was available on the potential for respiratory irritation of the notified chemical.

In a mouse Local Lymph Node Assay, the notified chemical showed no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation.

Repeated dose toxicity
A NOAEL of 50 mg/kg bw/day was determined from a 28 day repeated dose (oral – gavage) toxicity test in rats, based on no effects at this highest dose tested. No test substance-related, relevant findings were observed with regard to body weight parameters at all dose level in all animals. However, histopathological investigation of the testis revealed a minimal tubular degeneration and a minimal luminal debris in the corresponding epididymidal tubules in 2 (out of 5) animals at 50 mg/kg bw/d dose. Due to the minimal grade of severity and the low numbers of affected animals, it could not be clarified in total if these findings represented a treatment-related effect or a spontaneous background lesion. Moreover, the sperm analyses performed in all individuals of test group 12 did not reveal any test substance-related effects.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation assay and was not considered to be genotoxic in an in vitro mammalian cell gene mutation test nor in an in vitro micronucleus test in V79 cells.

Toxicity for reproduction
In a Modified One-Generation Reproduction Toxicity Study in Wistar Rats Oral Administration (Gavage), the NOAEL for systemic toxicity, reproductive and developmental effects was set at 50 mg/kg bw/day, which was the highest dose tested .

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

Hazard classification	***Hazard statement***
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided, the notified chemical is expected to be a skin irritant.

Reformulation
Transport, storage and reformulation workers may have dermal contact with the notified chemical at up to 100% concentration. Accidental ocular exposure is also possible. At up to 100% concentration there is a potential for irritation effects. 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 products containing the notified chemical to clients (e.g., hairdressers and beauty salon workers) or the use of household

products in the cleaning industry may be exposed to the notified chemical at < 0.2% 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 may experience repeated exposure to the notified chemical through the use of cosmetic and household products (containing the notified chemical at < 0.2% in individual products). The main route of exposure is expected to be dermal with some potential for inhalation and for accidental ocular or oral exposure.

Local effects

The notified chemical is irritating to the skin and slightly irritating to the eyes. However, given the relatively low proposed use concentration (< 0.2%), significant irritation effects are not expected.

Systemic effects

The potential systemic exposure to the public from the use of the notified chemical in cosmetics and household products was estimated to be 0.4802 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 50 mg/kg bw/day, which was derived from an oral (gavage) repeated dose toxicity study, the margin of exposure (MoE) was estimated to be 104. A MoE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at < 0.2% in cosmetics and household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of finished fragrance oils for reformulation into cosmetic and household products. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

The fragrance formulations containing the notified chemical will be blended with other ingredients in the manufacture of cosmetic and household products within a fully enclosed environment. The process is expected to be followed by automated filling of the formulated products into containers of various sizes suitable for retail and use. Wastes containing the notified chemical generated during reformulation include equipment wash water, empty import containers and spilt materials. Empty import containers and wash waters are expected to be recycled during subsequent blending processes or released to sewers, or disposed of to landfill in accordance with local government regulations. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

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 across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to be released to sewers on a nationwide basis. The notified chemical is not readily biodegradable (5% in 28 days). For the details of the environmental fate studies, please refer to Appendix C.

The half-life of the notified chemical in air is calculated to be 2.4 h based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA 2011). Therefore, if released to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleaning products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that there is no removal of the notified chemical during sewage treatment processes**.**

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	2,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	2,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	5.48	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:	1.12	µg/L
PEC - Ocean:	0.11	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 1.124 µg/L may potentially result in a soil concentration of approximately 0.0075 mg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 0.037 mg/kg and 0.075 mg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 81.5 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 72.1 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 = 101 mg/L	Not harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 640 mg/L	Not inhibitory to microbial respiration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is considered to be harmful to fish and aquatic invertebrates and is formally classified as ‘Acute Category 3: Harmful to aquatic life’. On the basis of the acute toxicity and the lack of ready biodegradability, the notified chemical is classified ‘Chronic Category 3: Harmful to aquatic life with long lasting effects’.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive acute endpoint for aquatic invertebrates and assessment factor of 100 given three acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Daphnia	72.1	mg/L
Assessment Factor	100	

Mitigation Factor	1	
PNEC:	721	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	1.12	721	0.001
Q - Ocean:	0.11	721	0.0001

The Risk Quotients (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemical have been calculated to be < 1 for both river and ocean compartments indicating that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on their maximum annual importation quantity. The notified chemical is not expected to bioaccumulate. On the basis of the PEC/PNEC ratio and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 10 °C

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined using a differential scanning calorimeter
Test Facility	BASF (2014a)

Boiling Point 244.9 °C at 101.3 kPa

Method	OECD TG 104 Boiling Point
Remarks	Determined by dynamic vapour pressure measurement
Test Facility	BASF (2014a)

Density 899 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 by an oscillating density meter. The dynamic viscosity (η) was measured by a rotational viscometer with cone plate geometry.
Test Facility	BASF (2014a)

Vapour Pressure 1.0×10^{-3} kPa at 20 °C
2.2×10^{-3} kPa at 25 °C
3.0×10^{-2} kPa at 50 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Determined by the gas saturation method. Vapour pressures were calculated using a molar mass of 200.37 g/mol.
Test Facility	BASF (2014a)

Water Solubility 0.57 g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method
Test Facility	Institut Kuhlmann (2013)

Surface Tension 51 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions EC Council Regulation No 440/2008 A.5 Surface Tension
Remarks	The test was conducted at 90% saturation concentration.
Test Facility	BASF (2015a)

Adsorption/Desorption – screening test log Koc = 2.44 at 23 °C

Method	OECD TG 121 estimation of the adsorption coefficient (Koc) using high performance liquid chromatography (HPLC).
Remarks	Due to interference peak of the solvent, some of the reference materials were measured as single measurements.
Test Facility	BASF (2015b)

Flash Point 105.5 °C

Method	Flashpoint according DIN EN ISO 2719, method A (comparable to ASTM D 93)
Remarks	Closed cup equilibrium method. Determined by heating the sample of the notified chemical

	in a closed crucible; Then while the temperature is slowly increased, the vapour/air mixture is ignited with an ignition flame introduced through a cover aperture.
Test Facility	BASF (2012)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.12 Flammability (Contact with Water) UN Recommendations on the Transport of Dangerous goods, Manual of Tests and Criteria, 5th revised version, Part III, Test N.3 (section 33.3.1.5)
Remarks	The test was determined whether the reaction of the substance with water leads to the development of dangerous amounts of highly flammable gases. The substance is tested according to a step by step sequence. If ignition occurs at any step no further testing is necessary. The gas evolution was measured by displacement of the liquid in a graduated cylinder. The test substance was also tested for its pyrophoric properties in contact with air. It was added to an inert carrier and then brought in contact with air at ambient temperatures for 5 minutes.
Test Facility	BASF (2015c)

Autoignition Temperature 185°C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	The auto-ignition temperature tests of flammable gases or vapours were performed at an atmospheric pressure of 1005 mbar-102 mbar. The corrected auto temperature of 185 °C was obtained from three test runs and performed according to EN 14522.
Test Facility	BASF (2015d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Wistar / Crl:WI (Han)
Vehicle	The test substance administered as supplied
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	There were no deaths observed during the study period. Effects observed in animals included; impaired general state, piloerection, salivation, cowering position, dyspnoea, apathy, stagger and exophthalmos.
Effects in Organs	There were no remarkable necropsy findings
Remarks - Results	Body weight gains were within the normal range, with the exception of one animal, which showed stagnation of body weight gain during the second post-exposure week.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Bioassay (2013)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test
Species/Strain	Rat/ Wistar / Crl:WI (Han) SPF
Vehicle	The test substance administered as supplied
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	There were no deaths observed during the study period. No sign of toxicity local effects was observed.
Signs of Toxicity - Systemic	No sign of systemic toxicity effects was observed.
Effects in Organs	The body weight of all animals increased within the normal range throughout the study period.
Remarks - Results	No macroscopic pathologic abnormalities were observed in all animals examined at the end of the study.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.

TEST FACILITY Bioassay (2016a)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 403 Acute Inhalation Toxicity – Limit Test
EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation) – Limit Test

Species/Strain	Rat/Wistar/CrlGlxBrlHan:WI
Vehicle	The test substance administered as supplied
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	Liquid aerosol.
Particle Size	Mass median aerodynamic diameters (MMADs) of 2.3 and 2.2 µm.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (units)*		*Mortality*
		Nominal	*Actual*	
1	5 M	13.8 mg/L	5.2 mg/L	0/5
2	5 F	13.8 mg/L	5.2 mg/L	0/5

LC50	> 5.2 mg/L/4 .hours
Signs of Toxicity	There were no deaths observed during the study period. However, red encrusted nose, abdominal respiration indicating a local irritation effect, piloerection, and substance contaminated fur were observed after exposure and persisted for a maximum of 1 day.
Effects in Organs	Mean male body weights decreased on the first day post exposure, but otherwise unaffected by treatment. The mean body weights of the female animals were not affected by treatment.
Remarks - Results	No gross pathological abnormalities were noted at the end of the study.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY BASF (2016a)

B.4. Irritation – skin (*in vitro* EpiDerm)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test
OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method
EC Council Regulation No 440/2008 B.40 BIS. *In vitro* Skin Corrosion - Human Skin Model Test - reconstructed three dimensional human epidermis model (EpiDerm™)

Vehicle	The test substance administered as supplied
Remarks - Method	A single topical application of 50 µL (corrosion test) or 30 µL (irritation test) of the undiluted test substance were added to a reconstructed three dimensional human epidermis model (EpiDerm™). Corrosion Test: Incubation of two EpiDerm tissue samples with the test substance for three minutes and one hour. Irritation Test: Incubation of three EpiDerm tissue samples with the test substance for one hour followed by 42 hours post incubation. Colorimetric test was performed to measure the metabolic activity of the destructed tissue.

RESULTS

Corrosion test

Test material	*Mean OD_{570} of duplicate tissues – Exposure 3 min*	*Relative mean Viability (%)*	*Mean OD_{570} of duplicate tissues – Exposure 1 hour*	*Relative mean Viability (%)*
Negative control	2.629	100	2.366	100
Test substance	2.382	91	2.684	113
Positive control	0.273	10	0.125	5

OD = optical density

Irritation test

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	2.734	100	7.39
Test substance	0.237	9	4.58
Positive control	0.061	2	0.21

OD = optical density; SD = standard deviation

Remarks - Results

The test substance was not able to reduce MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) directly.

Corrosion test: the mean viability of the test-substance treated tissues determined after an exposure period of 3 minutes was 91%, and it was 113% after an exposure period of 1 hour.

Irritation test: the mean viability of the test-substance treated tissues determined after an exposure period of 1 hour with about 42 hours post-incubation was 9%.

CONCLUSION

The notified chemical was irritating to the skin under the conditions of the test.

TEST FACILITY

BASF (2013)

B.5. Irritation – eye

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 405 Acute Eye Irritation/Corrosion
EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation)

Species/Strain: Rabbit/New Zealand White: Hsdlf:NZW – Harlan (SPF)
Number of Animals: 3
Observation Period: 1, 24, 48 and 72 hours and 7 days
Remarks - Method: No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	1	0.7	0.3	1	< 7 day	0
Conjunctiva: chemosis	0.7	0.3	0.3	1	< 72 hours	0
Conjunctiva: discharge	0	0	0	2	< 24 hours	0
Corneal opacity	0	0	0	0	Not observed	0
Iridial inflammation	0.3	0	0	1	< 48 hours	0

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

Remarks - Results

Conjunctival irritation was present in all animals at the 1 and 24 hour observations, in two animals at the 48 hour observation and just one

animal at the 72 hour observation with all effects resolved at the 7 day observation. Iridial irritation was seen in one animal at the 1 hour and 24 hour observations.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Bioassay (2012)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain	Mouse/ BALB/c
Vehicle	Acetone:olive oil (4:1, v/v).
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-Hexylcinnamaldehyde .
Remarks - Method	

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	338.9	1.00
25	5 F	467.7	1.38
50	5 F	668.1	1.97
100	5 F	774.3	2.28
Positive Control			
5%	5 F	448.6	1.5
10%	5 F	585.0	1.9
25%	5 F	1715.0	5.7

Remarks - Results The animals did not show any signs of systemic toxicity during the course of the study and no cases of mortality were observed.

Erythema (grade 1) was seen on the ears of rabbits where the undiluted test material had been applied.
The body weight of the animals was within the range commonly recorded for animals of this strain and age. A statistically significant increase in ear weights was observed in all treatment groups.

The EC3 value could not be calculated, since none of the tested concentrations induced a S.I. greater than the threshold value of 3.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY Harlan (2013)

B.7. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral)

Species/Strain	Rats/Wistar
Route of	Oral – gavage

Administration	
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: No recovery group information was sighted
Vehicle	None
Remarks - Method	In a preliminary test, the test substance was administered to groups of 5 male and 5 female Wistar rats by gavage at dose levels of 0 (vehicle control), 200, and 600 mg/kg bw/day. Due to reduced food consumption and severe body weight loss in all animals of the test groups (200 and 600 mg/kg bw/d) they were euthanised on day 25. The dose level for the main test was selected to be 0, 10 and 50 mg/kg bw/d.

RESULTS

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

Mortality and Time to Death

No mortality was observed during the period of the test.

Clinical Observations

No test substance-related, findings were observed with regard to body weight parameters (food consumption and body weight gain) at all dose levels.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There was a statistically significant ($p \leq 0.05$) increase (1.57%) in the mean corpuscular haemoglobin concentration in male rats in the 50 mg/kg bw/day dose group. A statistically significant ($p \leq 0.05$) reduction in lymphocytes (25.4%) was also seen in male rats in the 50 mg/kg bw/day dose group, with female rats showing a statistically significant ($p \leq 0.05$) reduction in lymphocytes (40.4%), but only in the 10 mg/kg bw/day group with no reduction at the higher dose. Statistically significant ($p \leq 0.05$) reductions in white blood cells, total protein and albumin were observed in female animals in the 10 mg/kg bw/day group, and a statistically significant ($p \leq 0.05$) increase was seen in eosinophils in male animals in the 10 mg/kg bw/day group. None of the changes seen in the 10 mg/kg bw/day group showed a dose response relationship as animals in the 50 mg/kg bw/day group had levels similar to the control animals. No other test substance-related findings with regard to haematology and clinical chemistry were observed.

Effects in Organs

There were no treatment related changes noted during gross pathological examinations, and organ weights determination. Sperm analysis did not show any abnormalities. The histopathological investigation of the testis revealed a minimal tubular degeneration and a minimal luminal debris in the corresponding epididymidal tubules in 2 (out of 5) animals at 50 mg/kg bw/day dose.

Remarks – Results

The changes in the mean corpuscular haemoglobin concentration and lymphocytes are not considered to be treatment related as they were either very slight or showed no dose response relationship when both sexes were considered. The study authors recommended a further reproductive study (B11 below) to determine the relevance of the minimal tubular degeneration and minimal luminal debris seen in two animals to treatment by the test substance.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on an absence of treatment related adverse effects at this highest dose.

TEST FACILITY BASF (2015e)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Pre incubation procedure and standard plate test
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, and *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 3.3 µg – 5,000 µg/plate b) Without metabolic activation: 33 µg – 5,000 µg/plate
Vehicle	DMSO
Remarks - Method	No significant protocol deviations. Plate Pre incubation method

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5,000			
Test 1		≥ 5,000	> 5,000	Negative
Test 2		≥ 1,000	> 5,000	Negative
Present	> 5,000			
Test 1		≥ 5,000	> 5,000	Negative
Test 2		≥ 333	> 5,000	Negative

Remarks - Results	No substantial increase in revertant colony numbers of any of the tester strains were observed following treatment with the notified chemical at any dose level, with or without metabolic activation, in either mutation test. No precipitation of the test substance was found. The concurrent positive control compounds demonstrated the sensitivity of the assay and the metabolising activity of the liver preparations.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	BASF (2013b)

B.9. Genotoxicity – *in vitro* Gene Mutation Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test EC Directive No 440/2008; B.17 Mutagenicity - *In vitro* Mammalian Cell Gene Mutation Test
Species/Strain	Chinese hamster ovary (CHO) cells
Cell Type/Cell Line	(CHO) cells
Metabolic Activation System	S9 mix from phenobarbital- and β-naphthoflavone induced rat liver (exogenous metabolic activation).
Vehicle	Ethanol
Remarks - Method	No significant protocol deviations. The cultures were incubated for the respective exposure period at 37°C, 5% (v/v) CO2 and ≥ 90% relative humidity

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*
Absent			
Test 1	0*, 9.4*, 18.8*, 37.5*, 75.0*, 150.0*, 300.0, 600.0	4 hours	7-9 days
Test 2	0*, 6.3, 12.5*, 25.0*, 50.0*, 100.0*, 200.0*, 400.0	4 hours	7-9 days
Present			
Test 1	0*, 18.8*, 37.5*, 75.0*, 150.0*, 300.0*, 600.0, 1200.0	4 hours	7-9 days

Test 2	0*, 12.5*, 25.0*, 50.0*, 100.0*, 200.0*, 400.0, 800.0	4 hours	7-9 days

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 262.5	> 600	≥ 300.0	Negative
Test 2		> 400	≥ 400.0	Negative
Present				
Test 1	≥ 525.0	> 1200.0	≥ 600.0	Negative
Test 2		> 800.0	≥ 400.0	Negative

Remarks - Results

The vehicle controls indicated mutant frequencies within the range expected for the CHO cell line.

Both positive control substances, ethyl methanesulfonate (EMS) and 7,12-dimethylbenz[a]-anthracene (DMBA), showed the expected increase in the frequencies of forward mutations.

In the test 1 & 2, the highest concentrations evaluated for gene mutations were clearly cytotoxic in the absence and the presence of metabolic activation.

CONCLUSION

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

TEST FACILITY

BASF (2016b)

B.10. Genotoxicity – *in vitro* Micronucleus Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 487 *In vitro* Micronucleus Assay in V79 Cells (Cytokinesis Block Method)
EC No 640/2012; B.49

Species/Strain: Chinese hamster/V79 cells

Route of Administration: The test substance was applied up to clearly precipitating concentrations in culture medium.

Vehicle: 1% [v/v] ethanol

Physical Form: Liquid

Remarks - Method: No significant protocol deviations. The metabolic Activation System was S9 mix from phenobarbital/β-naphthoflavone induced rat liver (exogenous metabolic activation).

The preliminary test was performed following the method described for the main experiment. As indication of test substance toxicity relative population doubling (RPD) and cell attachment / morphology were determined for dose selection.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 15.6, 31.3, 62.5*, 125.0*, 250.0*, 500.0	4 hours	24 hours
Test 2	0*, 15.6, 31.3*, 62.5*, 125.0*, 250.0, 500.0	24 hours	24 hours
Present			
Test 1	0*, 15.6, 31.3, 62.5*, 125.0*, 250.0*, 500.0	4 hours	24 hours
Test 2	0*, 15.6, 31.3, 62.5*, 125.0*, 250.0*, 500.0	4 hours	44 hours

Test 3	0*, 50.0, 75.0*, 100.0*, 150.0*, 200.0, 300.0	4 hours	24 hours
Test 4	0*, 50.0*, 75.0*, 100.0*, 150.0*, 200.0*, 300.0	4 hours	44 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 131.3	≥ 500	≥ 250.0	Negative
Test 2	≥ 262.5	≥ 250.0	≥ 125.0	Negative
Present				
Test 1	≥ 65.6	≥ 500	≥ 250.0	Negative
Test 2		≥ 500	≥ 250.0	Negative
Test 3		≥ 300	≥ 200.0	Negative
Test 4		≥ 300	≥ 300.0	Negative

Remarks - Results

Cytotoxicity indicated by clearly reduced cell count (showed by relative population doubling) or proliferation index (CBPI) was observed at least at the highest applied test substance concentration in all experimental parts of this study.

The test substance did not cause any biologically relevant increase in the number of cells containing micronuclei without metabolic activation. In the presence of metabolic activation several single indications for a genotoxic potential of the test substance were obtained, although all the necessary criteria were not fulfilled for the test substance to be clearly positive or negative. In experiments 2 and 4 with metabolic activation a statistically significant increase in the number of micronucleated cells was observed. In experiment 4 the values were within the historical control range and showed no dose response relationship and the study authors argued that therefore they should be regarded as biologically irrelevant. In experiment 2 a statistically significant increase was only seen at the highest evaluated concentration of 250 µg/mL, but the study authors surmise that this may have been due to test substance precipitates in the culture medium at this concentration. The increases in micronucleus frequencies were only weak with low values and were considered as biological variability.

The vehicle controls indicated frequencies of micronucleated cells within our historical negative control data range (95% control limit) for V79 cells.

Both positive control substances, ethyl methanesulfonate (EMS) and cyclophosphamide (CPP), showed the expected increase in the number of cells containing micronuclei.

CONCLUSION

The notified chemical was not clastogenic under the conditions of this *in vitro* Micronucleus Test.

TEST FACILITY

BASF (2016c)

B.11. Toxicity to reproduction – one generation study

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 415 & 416 Modified One-Generation Reproduction Toxicity Study in Wistar Rats Oral Administration (Gavage)
EC 440/2008

Species/Strain	Rat/Wistar Crl:WI(Han)
Route of Administration	Oral – gavage
Exposure Information	Exposure period: Daily
Vehicle	Corn oil
Remarks – Method	The test substance was given daily to groups of 25 male and 25 female Wistar rats. At least 69 days after the beginning of treatment, F0 animals were mated. Animals were allowed to deliver and rear their pups (F1 generation pups) until postnatal days (PND) 4 or 21, when the offspring was necropsied. The male F0 generation parental animals were sacrificed during rearing of the F1 generation pups. The female F0 generation parental animals were sacrificed after weaning of the F1 generation pups.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
control	25M, 25F	0	1/50
low dose	25M, 25F	5	0/50
medium dose	25M, 25F	15	0/50
high dose	25M, 25F	50	2/50

Mortality and Time to Death

One female animal in the control group was euthanised on PND 6 due to severe laboured respiration. Two female animals in the 50 mg/kg bw/day group were found dead on PND 11 and 15, with indication of substance aspiration. None of the deaths were considered by the study authors to be attributable to the toxicity of the test substance.

Effects on Parental (P) animals:

There was a dose response relation seen across the dose groups with greater incidence of salivation at higher doses.

There was a statistically significant decrease in food consumption in female animals in the 50 mg/kg bw/day dose group during lactation of 15% below the control value. Other statistically significant food consumption decreases were observed in the treatment groups but they were either isolated or showed no dose response relationship.

There were statistically significant lower body weights in comparison to the control in female animals in the 50 mg/kg bw/day dose group on gestation day (GD) 20 (6.6%), PND 4 (7.9%), 7 (7.7%) and 14 (5.9%). A statistically significant lower bodyweight was also seen in female animals in the 15 mg/kg bw/day dose group on GD 7 (4.9%), 14 (5.2%) and 20 (6.2%) and during the lactation phase on PND 0 (5.4%) and 4 (4.8%).

Male and female fertility indexes did not show any adverse treatment related effects. The numbers of implantation sites showed a slight decrease in the treatment groups which was statistically significant in the 5 and 50 mg/kg bw/day dose groups with decreases of 14 and 23% respectively. The number of pups delivered was statistically significant lower in all three treatment groups by 12.5%, 8.9% and 16% for the 5, 15 and 50 mg/kg bw/day dose groups respectively and hence the number of live born pups was decreased by similar amounts. The number of still born pups was not affected. The study authors noted that there were no morphological correlations observed in male or female parent animals and thus no evidence that the lower implantation and birth numbers are a treatment related effect.

There were no treatment related changes in haematology, clinical chemistry or sperm parameters. There were no organ weight changes that were considered to be related to treatment of the test substance.

A statistically significant increase in the number of animals (9/25 vs 2/25) with tubular degeneration of the left testis was observed in the 50 mg/kg bw/day dose group in comparison to the control group. However in the 50 mg/kg bw/day dose group the severity of the effects was minimal while in the control group they were more severe and the study authors considered the tubular degeneration to be an incidental finding.

Effects on 1st Filial Generation (F1)

In the 50 mg/kg bw/day dose group there was a statistically significant lower pup body weight during PND 7 -

21 (up to 17% below control), as well as decreased pup body weight gain during PND 4 – 21. There were also decreased spleen and thymus weights for pups in the same group and increased relative brain weights that are likely to be secondary to the lower bodyweight.

No test substance-related adverse findings were reported for offspring of the 15 or 5 mg/kg bw/day dose groups.

Remarks - Results

The No Observed Adverse Effect Level (NOAEL) for general, systemic toxicity was established by the study authors as 5 mg/kg bw/day for the F0 parental rats, based on reduced food consumption and/or reduced body weight gain. The NOAEL for fertility and reproductive performance for the F0 parental rats was established by the study authors as 50 mg/kg bw/day, the highest dose tested. The NOAEL for developmental toxicity in the F1 progeny was established by the study authors as 15 mg/kg bw/day, based on slightly decreased pre-weaning pup body weights/pup weight gain.

However, at all the doses there were no adverse treatment related effects aside from the lower bodyweight in female animals and their offspring. The lower bodyweight of the pups is considered to be secondary to that of the parent animals. The lower bodyweight of the parent animals is correlated with lower food consumption possibly due to the irritant nature of the test substance. If correlated to the lower food consumption the lower bodyweights cannot be considered to be as a result of the systemic toxicity of the test substance. Therefore the No Observed Adverse Effect Level (NOAEL) for systemic toxicity should be set at the highest dose tested.

CONCLUSION

Under the conditions of the present modified one-generation reproduction toxicity study the NOAEL for general, systemic toxicity, reproductive and developmental toxicity was set at the maximum tested dose based on a lack of treatment related systemic toxicity effects observed.

TEST FACILITY BASF (2016d)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical oxygen demand (BOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	0	7	64
14	0	14	81
24	1	24	91
28	1	28	91.5

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, aniline, surpassed the threshold level of 60% by 14 days (81%), therefore, the tests indicate the suitability of the inoculum. The pH values in the test assays with test substance and mineral medium was in the range from pH 6 to 8.5 at the end of exposure The test substance attained 1% biodegradation after 28 days and, therefore, cannot be considered to be readily biodegradable under the terms of OECD Guideline 301C(I).
CONCLUSION	The notified chemicals are not readily biodegradable.
TEST FACILITY	BASF (2014b)

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemicals
METHOD	OECD TG 302 C Inherent Biodegradability: Modified MITI Test (II)
Inoculum	Sewage sludge
Exposure Period	28 Days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical oxygen demand (BOD)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles

Results

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	4	7	67
14	5	14	80
24	7	24	85
28	4	28	84

Remarks – Results	All validity criteria for the test were satisfied. The percentage degradation

of the reference compound, sodium benzoate, surpassed the threshold level of 40% after 7 days (67%) and 60% by 14 days (80%), therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 6 days (38%; 35% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The test item attained 4% biodegradation after 28 days and, therefore, cannot be considered to be readily biodegradable under the terms of OECD Guideline 302C (II).

CONCLUSION The notified chemicals are not inherently biodegradable.

TEST FACILITY Bioassay (2016b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemicals

METHOD OECD TG 203 Fish, Acute Toxicity Test –Semi-static

Species	*Gobiocyprus rarus* (Chinese Rare Minnow)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Gas Chromatography (GC)
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Geometric mean measured concentration*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
60	47.3	7	0	0	0	0	0
75	56.9	7	0	0	0	0	1
95	75.7	7	0	0	0	1	2
120	95.1	7	0	1	7	7	7
150	118	7	0	7	7	7	7

LC50 81.5 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 96 h test period. The dissolved oxygen concentration was greater than 60% of the air saturation value (ASV) throughout the test duration. The geometric mean measured concentrations of the test substance were determined before and after renewal and at the start and end of the test period. These measured concentrations were not within ± 20% difference of the nominal concentrations. Therefore, the 96 h LC_{50} for fish was determined to be 81.5 mg/L, based on geometric mean measured concentrations.

CONCLUSION The notified chemicals are considered to be harmful to fish.

TEST FACILITY Bioassay (2016c)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemicals
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test - static
Species	*Daphnia magna* STRAUS
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	2.20 – 3.20 mmol/L
Analytical Monitoring	GC
Remarks - Method	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		*24 h [acute]*	*48 h [acute]*
Control	20	0	0
4.6	20	0	0
10	20	0	0
22	20	0	0
46	20	0	1
100	20	5	2
220	20	20	20

EC50	71.2 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The immobilization in the control was ≤10%. The oxygen concentration was > 3 mg/L in the control and test vessels. The actual concentrations of the test substance preparations were measured at the start and end of the 48 h test period. Since the mean of these measured notified chemical test medium concentrations remained within ± 20 % of the nominal concentrations, the effect values were based on the nominal concentrations of the notified chemical. The 48 h EC_{50} for *D. magna* was 71.2 mg/L, calculated using the Probit method (TOXRAT Professional 2.10) based on nominal concentrations.
CONCLUSION	The notified chemicals are considered to be harmful to aquatic invertebrates.
TEST FACILITY	BASF (2014c)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test - Static
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1, 3.2, 10, 32, and 100 mg/L Actual: 1.24, 3.9, 14.7, 45.8 and 162 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC - MS
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EyC50 *mg/L at 72 h*	*NOEC* *mg/L*	*ErC50* *mg/L at 72 h*	*NOEC* *mg/L*
61.5		101	

Remarks - Results

All validity criteria for the test were satisfied. The cell multiplication factor in the untreated control was > 16 in 72 hours. The cell multiplication factor in the untreated control was 383-fold after 72 hours.

The validity criterion for the mean coefficient of variation for section-by-section growth rates for each test day in the control cultures was ≤35%.

The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 2.2%.

The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at start and end of the 72 h test period. Since the mean of these measured notified chemical test medium concentrations remained within ± 20 % of the nominal concentrations, the effect values were based on the nominal concentrations of the notified chemical. The notified chemicals had ErC_{50} 101 mg/L. ECx values and confidence limits were calculated by Probit analysis.

CONCLUSION

The notified chemicals are not considered to be harmful to algae.

TEST FACILITY

BASF (2015f)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE

Notified chemicals

METHOD

OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum

Activated sewage sludge

Exposure Period

3 hours

Concentration Range

Nominal: 62.5-1000 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. 3,5-Dichlorophenol was used as the reference control.

RESULTS

IC50

640 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 640 mg/L, based on nominal concentrations.

CONCLUSION

The notified chemical is not inhibitory to microbial respiration.

TEST FACILITY

BASF (2013c)

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