File No.: LTD/2138

May 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Phenol, 2-methyl-, reaction products with 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane, hydrogenated

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 Agriculture, Water and the Environment.

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 on our website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2138	Symrise Pty Ltd	Phenol, 2-methyl-, reaction products with 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane, hydrogenated	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard Classification	*Hazard Statement*
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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

Hazard Classification	*Hazard Statement*
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, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

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

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

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

- 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:
  - Impervious gloves
  - Coveralls
  - Respiratory protection if aerosols or mists are expected to be generated.

  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.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

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.

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 final use concentration of the notified chemical exceeds 0.12% in cosmetic and household products;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
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 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
None

2. IDENTITY OF CHEMICAL

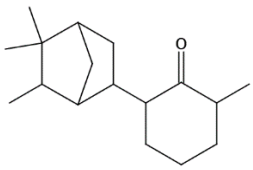
MARKETING NAME(S)
Aldron®

CAS NUMBER
2231434-98-1

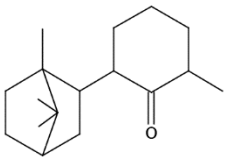
CHEMICAL NAME
Phenol, 2-methyl-, reaction products with 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane, hydrogenated

MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA
The notified chemical is a UVCB substance comprised mainly of isomers of the following substances:



Cyclohexanone, 2-methyl-6-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)- (CAS No. 17283-66-8)



Cyclohexanone, 2-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)- (CAS No. 93541-00-5)

MOLECULAR WEIGHT
248.4 g/mol

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

3. COMPOSITION

DEGREE OF PURITY
100% (UVCB)

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: clear colourless to yellow liquid

Property	***Value***	***Data Source/Justification***
Melting Point	-38 to -36 °C at 98.5 kPa	Measured
Boiling Point	325.9 °C at 101.3 kPa	Measured
Density	981.4 kg/m^3 at 20 °C	Measured
Vapour Pressure	4.6×10^{-5} kPa at 25 °C	Measured
Water Solubility	$0.619 - 0.626 \times 10^{-3}$ g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functional groups
Partition Coefficient (n-octanol/water)	log Pow = 5.17 - 6.04 at 20 °C	Measured
Adsorption/Desorption	log Koc = 3.83 - 3.86 (MCI method) log Koc = 4.11 - 4.13 (Kow method)	Calculated using EPIsuite
Dissociation Constant	Not determined	Contains no dissociable functional groups
Flash Point	161.5 °C at 101.3 kPa	Measured
Flammability	Combustible liquid	Based on measured flash point
Autoignition Temperature	320 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties

DISCUSSION OF PROPERTIES
For 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.

The notified chemical has a flash point of 161.5 ºC. Based on *Australian Standard AS1940* definitions for combustible liquid, a liquid that has a fire point which is both greater than 93 °C and is less than its boiling point is a Class C2 combustible liquid.

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 mostly as a component (≤ 0.12% concentration) of finished consumer products such as fine fragrances, other cosmetic products and household cleaning products. The notified chemical may also be imported into Australia as a fragrance formulation at ≤ 1% concentration, or in its neat form.

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

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

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
Symrise Pty Ltd

TRANSPORTATION AND PACKAGING
The fragrance formulations containing the notified chemical at ≤ 1% concentration will be mostly imported in lacquered-lined metal drums of 30 L or 216 L size and 30 L plastic canisters. The notified chemical introduced in neat form will be imported in 30 L lacquered-lined steel cans.

Finished consumer products containing the notified chemical at ≤ 0.12% concentration will be packaged in containers suitable for retail sales.

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

Finished Consumer Product	*Maximum Usage Concentration of the Notified Chemical (%)*
Fine fragrances	0.12
Other cosmetic products	0.02
Household cleaning products	0.01

OPERATION DESCRIPTION
Reformulation of the notified chemical or fragrance formulations containing the notified chemical at ≤ 1% concentration into finished consumer goods may vary depending on the type of product and may involve both automated and manual transfer steps. Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling of the reformulated end-use products into containers of various sizes.

End-use products containing the notified chemical at ≤ 0.12% concentration will be used by consumers and professionals such as hairdressers, beauticians and cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse	None	Incidental
Mixer	4	2
Drum handling	4	2
Drum cleaning/washing	4	2

Maintenance	4	2
Quality control	0.5	2
Packaging	4	2
End users (professionals)	1- 8	200

EXPOSURE DETAILS
Transport, storage and warehouse workers may come into contact with the notified chemical or products containing the notified chemical, only in the unlikely event of an accidental rupture of containers.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical in its neat form or at ≤ 1% concentration may occur during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of personal protective equipment (PPE) such as protective clothing, eye protection, impervious gloves and appropriate respiratory protection by workers.

End-use
Exposure to the notified chemical in end-use products (at ≤ 0.12% concentration) may occur in professions where the services provided involve the application of cosmetics to clients (e.g. hair dressers and workers in beauty salons), or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers are expected to be of a similar or lesser extent than that experienced by consumers using end-use products containing ≤ 0.12% the notified chemical.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 0.12% concentration through the use of a wide range of cosmetic and household products containing the notified chemical. The principal route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly if products are applied by spray.

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

Endpoint	***Result and Assessment Conclusion***
Acute oral toxicity – rat	LD50 > 2000 mg/kg bw; low toxicity
Skin irritation – *in vitro* (EpiDerm™ model)	non-irritating
Eye irritation – *in vitro* Bovine Corneal Opacity and Permeability (BCOP) test	non-irritating
Skin sensitisation – mouse local lymph node assay with BrdU-ELISA	evidence of sensitisation (EC1.6 = 14.8%)
Mutagenicity – bacterial reverse mutation	non-mutagenic

Toxicokinetics
Given its low molecular weight (248.4 g/mol), the notified chemical may be absorbed across the respiratory or gastrointestinal tract. Based on the low water solubility (0.619 - 0.626 mg/L at 20 °C) and high partition coefficient (log Pow = 5.17 - 6.04 at 20 °C), indicating a reasonably high lipophilicity, percutaneous absorption is expected to be limited.

No information was available for distribution, metabolism and excretion of the notified chemical.

Acute Toxicity
The notified chemical was found to be of low acute oral toxicity in rats.

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

Irritation and Sensitisation
The notified chemical was found to be non-irritating to the skin based on an *in vitro* study conducted using the reconstructed human epidermis model.

In an *in vitro* BCOP eye irritation test the notified chemical was determined to be non-irritating.

In an LLNA study, the notified chemical was considered a weak sensitiser and has been recommended for classification under GHS (see below). The notified chemical at 25% and 100% produced stimulation indices (SI) that were statistically significantly greater than the threshold of ≥ 1.6 for positive responses. The effective concentration inducing a SI of 1.6 (EC1.6) was established as 14.8%.

Repeated Dose Toxicity
No repeated dose toxicity data on the notified chemical were provided.

Mutagenicity/Genotoxicity
The notified chemical tested negative in a bacterial reverse mutation assay. No study was submitted for genotoxicity of the notified chemical.

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

Hazard Classification	***Hazard Statement***
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological information provided, the notified chemical is a weak skin sensitiser.

Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical at up to 100% concentration during reformulation. The use of local ventilation, enclosed/automated processes and PPE by workers (i.e., protective clothing, eye protection and impervious gloves and respiratory protection if inhalation exposure may occur) are expected to minimise the potential for exposure.

Therefore, provided control measures are in place to minimise worker exposure, 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 0.12% concentration, similar to public use. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the notified chemical is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment, see section 6.3.2 below.

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 up to 0.12% concentration.

Irritation and Sensitisation
The notified chemical is a weak skin sensitiser. Significant sensitisation effects are not expected from the use of products containing the notified chemical at the proposed low use concentration (up to 0.12%) in cosmetic and household products.

Systemic toxicity
Systemic exposure is expected to be limited by the low concentration of the notified chemical (up to 0.12%) in end use products.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at up to 0.12% concentration in cosmetic and household products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will mostly be imported into Australia as a component of end-use cosmetic and household products. It may also be imported in the neat form or as a component of fragrance solutions for reformulation into the end-use products. In general, the reformulation processes are expected to involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into end-use containers. Any accidental spills are expected to be collected and disposed of in accordance with local government regulations. Wash waters from reformulation equipment cleaning, containing the notified chemical are expected to be disposed of as trade waste.

RELEASE OF CHEMICAL FROM USE

A majority of the notified chemical is expected to be washed into sewers as a result of its use in various cosmetic, fine fragrances and household products where it will be treated in sewage treatment plants nationwide before being released into surface waters.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the notified chemical is expected to remain as residues in empty product containers. These containers are expected to be either recycled or disposed of to domestic landfill.

7.1.2. Environmental Fate

Following its use in cosmetic products and household cleaning products, the notified chemical is expected to be primarily released into the sewer system and treated at sewage treatment plants where it is expected to be efficiently removed by partitioning to sewage sludge with a minor amount volatilising into air. The notified chemical is not expected to be persistent in the atmosphere with an estimated half-life of 0.37 days (EPISuite). The notified chemical is not readily biodegradable (0% biodegradation after 28 days), for further details on the biodegradation study refer to Appendix C. The notified chemical is expected to have bioaccumulation potential due to its calculated BCF of 4051 – 8633 L/kg wet-wt and high log Pow (log Pow = 5.17 - 6.04).

Some of the notified chemical may also remain in the end use and bulk containers, which are either recycled or disposed of to landfill. A proportion of the notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation or disposed of to landfill. In landfill and soils, the notified chemical is expected to have low mobility based on its calculated log Koc (3.83-4.13). In surface waters, soils and landfill, the notified chemical is expected to eventually degrade through biotic and abiotic processes into water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the notified chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. The extent to which the notified chemical is removed from the effluent in STP processes based on the properties of the notified chemical has not been considered for this scenario, and therefore no removal of the notified chemical during sewage treatment processes, is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.386	million

Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 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 0.56 µg/L may potentially result in a soil concentration of approximately 3.745×10^{-3} 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 1.873×10^{-2} mg/kg and 3.745×10^{-2} 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*
Daphnia Toxicity	EL50 = 89 mg/L (WAF*)	Harmful to aquatic invertebrates
Algal Toxicity	EL50 > 100 mg/L (WAF*) NOEL = 15 mg/L (WAF*)	Not harmful to algal growth

*WAF: Water Accomdodated Fraction

Based on the above ecotoxicological endpoints for the notified chemical, the notified chemical is expected to be harmful to aquatic invertebrates. Therefore, the notified chemical is classified as 'Category 3 H402 – Harmful to aquatic life' according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009). The notified chemical is not readily biodegradable. Therefore, the notified chemical is formally classified under the GHS for its long-term hazard as 'Category 3 H412 – Harmful to aquatic life with long lasting effects.

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) was calculated based on the most sensitive acute endpoint for daphnia (EL50 = 89 mg/L) using an assessment factor of 500 as only two acute trophic endpoints are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Invertebrates).	89	mg/L
Assessment Factor	500	
Mitigation Factor	1	
PNEC:	178	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.56	178	< 0.01
Q - Ocean:	0.06	178	< 0.01

The risk quotient (Q=PEC/PNEC) has been calculated based on the worst-case assumption of complete release into the waterways with no removal in STPs. As the Q value is significantly less than 1, the notified chemical is unlikely to reach ecotoxicologically significant concentrations. Therefore, on the basis of the PEC/PNEC ratio, the notified chemical is not considered to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -38 to -36 °C at 98.5 kPa

Method	OECD TG 102 Melting Point/Melting Range EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature
Remarks	Determined using differential scanning calorimetry
Test Facility	Consilab (2017a)

Boiling Point 325.9 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point EC Council Regulation No 440/2008 A.2 Boiling Temperature
Remarks	Determined using differential scanning calorimetry
Test Facility	Consilab (2017a)

Density 981.4 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids EC Council Regulation No 440/2008 A.3 Relative Density
Remarks	Determined using the oscillating densitometer
Test Facility	Consilab (2017b)

Vapour Pressure 4.6×10^{-5} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Determined by effusion method using Knudsen cell
Test Facility	Consilab (2017c)

Water Solubility $0.619 - 0.626 \times 10^{-3}$ g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Flask Method; water solubility was found to be 0.619×10^{-3} g/L at low loading rate of 12 to 14 mg test item/L, and 0.626×10^{-3} g/L at high loading rate of 114 to 119 mg test substance/L.
Test Facility	IES (2017a)

Partition Coefficient (n-octanol/water) log Pow = 5.17 - 6.04 at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method; the results were based on six peaks representing > 90% of the test substance.
Test Facility	IES (2017b)

Flash Point 161.5 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Determined by a closed cup method (Pensky Martens)
Test Facility	Consilab (2017d)

Autoignition Temperature 320 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks	Conducted using a semi-automated ignition apparatus
Test Facility	Consilab (2017e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute Oral Toxicity – Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Limit Test (2001)
Species/Strain	Rat/Sprague-Dawley (Crl:CD(SD)) (female)
Vehicle	Corn oil
Remarks – Method	No protocol deviation. Animals were dosed by gastric intubation. Based on the information supplied by the study sponsor (Symrise AG), 2,000 mg/kg was selected as the starting dose.

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 (highest dose tested)
Signs of Toxicity	Mucous stool was noted in two animals (one in each group) on day 1, and appeared normal on day 2.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks – Results	A decrease in body weight was noted in one animal in group 1 on day 3, returning to normal from day 7. As there were no associated clinical signs or necropsy findings, these effects were not considered related to the test substance by study authors.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	Biotoxtech (2017a)

B.2. Skin Irritation – *In Vitro* EPIDERM™ Skin Irritation Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2015) EpiDerm™ Reconstructed Human Epidermis Model
Vehicle	None
Remarks – Method	A variation of pre-incubation period from the study plan was not considered to have affected the integrity or validity of the study. In pre-tests, the test substance did not have any interference with MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazoliumbromide) reduction or with the test colour change. Positive and negative controls were run in parallel with the test substance: - Negative control: Dulbecco's Phosphate Buffered Saline (DPBS) - Positive control: sodium dodecyl sulphate (5% aqueous)

RESULTS

Test Material	*Mean OD_{570} of Triplicate Tissues*	*Relative Mean Viability (%)*	*SD of Relative Mean Viability*
Negative control	1.415	100.0	1.3
Test substance	1.064	75.2	3.0
Positive control	0.059	4.2	4.9

OD = optical density; SD = standard deviation

Remarks – Results	The positive and negative controls performed as expected and the standard deviation of the relative mean viability of the test substance-treated tissues was within acceptable range, confirming the validity of the test system.
CONCLUSION	Based on the mean tissue viability of > 50%, the notified chemical is not classified as a skin irritant according to the GHS criteria.
TEST FACILITY	Envigo (2017a)

B.3. Eye Irritation – *In Vitro* Bovine Corneal Opacity and Permeability Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (2013)
Vehicle	None
Remarks – Method	No protocol deviation. Minimum essential medium (MEM) was used instead of Eagle's MEM (EMEM), which is recommended in the OECD guidelines. The author stated that MEM is equivalent to EMEM in composition and osmolality, and thus could be used without restrictions. Positive and negative controls were run in parallel with the test substance: - Negative control: sodium chloride (0.9% w/v in water) - Positive control: 2-ethoxyethanol

RESULTS

Test Material	*Mean Opacities of Triplicate Tissues*	*Mean Permeabilities of Triplicate Tissues*	*IVIS*
Vehicle control	0.00	0.049	0.74
Test substance	0.33*	0.016*	0.57*
Positive control	64.00*	1.309*	83.64

IVIS = in vitro irritancy score
* Corrected for background values

Remarks – Results	The positive and negative controls performed as expected, confirming the validity of the test system. The IVIS for the test substance was < 3, indicating that the test substance did not require classification for eye irritation.
CONCLUSION	The notified chemical was not considered an eye irritant under the conditions of the test.
TEST FACILITY	Envigo (2017b)

B.4. Skin Sensitisation – LLNA

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 442B Skin Sensitisation: Local Lymph Node Assay BrdU-ELISA (2010)
Species/Strain	Mouse/CBA/N
Vehicle	Acetone: olive oil (4:1 v/v)
Preliminary study	Yes

Positive control	α-Hexylcinnamaldehyde, conducted in parallel with the test substance
Remarks – Method	No protocol deviation. A preliminary test was conducted using 5%, 10%, 25%, 50% and 100% of test substance to justify the dose concentrations for the main study.

RESULTS

Concentration (% w/w)	*Number and Sex of Animals*	*BrdU labelling index*	*Stimulation Index (test/control ratio)*
Test Substance			
0 (vehicle control)	5 F	0.25	1.00
2.5	5 F	0.27	1.09
25	5 F	0.51	2.02
100	5 F	0.71	2.84
Positive Control			
25	5 F	0.52	2.06

EC1.6	14.8%
Remarks – Results	The stimulation indices (SI) of the notified chemical at 25% and 100% were statistically significantly greater than the threshold of 1.6, indicating a sensitising response. No mortalities or abnormal clinical signs were noted in the test or control animals. Body weight changes of test and control animals between day 1 and 6 were comparable. Statistically significant increase in the mean erythema scores were observed in test animals at 25% concentration on days 4-6 and at 100% concentration on days 2-6. Statistically significant increase in the mean ear thickness was observed in test animals at 25% concentration on day 6 and at 100% concentration on days 3 and 6. Treatment related increase in the mean ear weight was noted at all test concentrations; however, the change was only statistically significant at 100% concentration. The positive and negative controls performed as expected, confirming the validity of the test.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.
TEST FACILITY	Biotoxtech (2017b)

B.5. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Plate incorporation (Test 1) and pre incubation procedures (Test 2 and 2a)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100; and *Escherichia coli*: WP2 uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	Test 1 With and without metabolic activation: 0, 3, 10, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate

Test 2
a) With and without metabolic activation (TA1535, TA100, WP2 uvrA): 0, 10, 33, 100, 333, 1,000, 2,500; and 5,000 µg/plate
b) With and without metabolic activation (TA1537): 0, 33, 100, 333, 1,000, 2,500 and 5,000µg/plate

Test 2a
a) Without metabolic activation (TA1537): 0, 33, 100, 333, 1,000, 2,500 and 5,000µg/plate
b) With and without metabolic activation (TA98): 0, 10, 33, 100, 333, 1,000, 2,500, and 5,000 µg/plate

Vehicle: Ethanol

Remarks – Method: No protocol deviation. A preliminary test was conducted and reported as Test 1. Due to a technical error, Test 2 with strain TA98 was repeated in Test 2a. TA1537 (without metabolic activation) was also repeated in Test 2a to evaluate the relevance of a dose-dependent result of Test 2.

Positive control:
With metabolic activation: 2-aminoanthracene (all strains)
Without metabolic activation: sodium azide (TA1535; TA100), 4-nitro-o-phenylene-diamine (TA1537; TA98), methyl methane sulfonate (WP2 uvrA).

RESULTS

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

Remarks – Results: In Test 2, a dose-dependent increase in the frequency of revertant colonies was observed in TA1537 (without metabolic activation). The number of colonies did not reach or exceed the threshold of thrice the number of the corresponding solvent control. In Test 2a, the observed increase was not repeated. Based on these results, the study authors stated that the increase in revertant colonies of this strain in Test 2 was considered biologically irrelevant.

For all other strains tested, no significant increase in the frequency of revertant colonies were observed at any dose of the test substance, with or without metabolic activation.

The positive and negative controls gave a satisfactory response, confirming the validity of the test system.

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

TEST FACILITY: Envigo (2017c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready Biodegradability

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from a domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	COD
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was directly added to the test medium in the test vessels. Sodium benzoate was used as a reference substance. A toxicity test was also run.

RESULTS

Test Substance		*Sodium benzoate*		*Toxicity Test*	
Day	*% Degradation*	*Day*	*% Degradation*	*day*	*% Degradation*
0	0	0	0	0	0
3	0*	3	68	3	28
14	0*	14	87	14	35
21	0*	21	90	21	36
28	0*	28	91	28	36

* Negative values were corrected to zero.

Remarks – Results	All validity criteria were met. The difference in extremes between replicates was less than 20%, the oxygen uptake of the inoculum blank was 17 mg/L and the pH was maintained between 7.4 and 7.8. The toxicity test indicated that the test substance was not considered inhibitory as the control sample reached 35% degradation after 14 days.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	IES (2017c)

C.2. Ecotoxicological Investigations

C.2.1. Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography with Flame Ionisation Detection (GC-FID) only for 50 mg/L and 100 mg/L loading rates
Remarks – Method	A definitive test was conducted based on a range finding study with no major deviations from the test guidelines. Each test loading rate was prepared individually and stirred for 96 hours. After that, the emulsions were filtered and the filtrates were tested as water accommodated fractions (WAFs). A reference test with potassium dichromate was conducted as part of a biannual quality assurance program.

RESULTS

Concentration (mg/L) Nominal loading rate	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0	0
6.25	20	0	0
12.5	20	0	0
25	20	0	0
50	20	0	0
100	20	8	12

LL50 89 mg/L at 48 hours

Remarks – Results All validity criteria were met. The dissolved oxygen was maintained at > 8 mg/L. The measured concentrations in freshly prepared samples were 0.512 mg/L for loading rate of 50 mg/L and 0.936 mg/L for loading rate of 100 mg/L. The EC50 of potassium dichromate in the reference test was within the expected range.

CONCLUSION The test substance is harmful to aquatic invertebrates.

TEST FACILITY IES (2017d)

C.2.2. Algal Growth Inhibition Test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
EC Council Regulation No 2016/266 C.3 Algal Inhibition Test

Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 15, 30, 45, 67,100 mg/L (WAF)
Initial measured: 0.36, 0.69, 1.1, 1.2 and 1.0 mg/L
Auxiliary Solvent None
Analytical Monitoring GC-FID
Remarks – Method A definitive test was conducted based on a range finding study with no major deviations from the test guidelines. Each test loading rate was prepared individually and stirred for 96 hours. After that, the emulsions were filtered and the filtrates were tested as water accommodated fractions (WAFs). A reference test with potassium dichromate was conducted as part of a biannual quality assurance program.

RESULTS

Growth rate		*Yield*	
ErL50 (mg/L)	*NOEL (mg/L)*	*EyL50 (mg/L)*	*NOEL (mg/L)*
>100	15	> 100	15

Remarks – Results The reference study indicated an ErC50 of potassium dichromate of 1.0 mg/L, which was within the expected range.

All validity criteria were met. The control cell density increased by a factor of 221, the mean coefficient of variation for section-by-section specific growth was 15% and the coefficient of variation for the average specific growth rates was 0.8%.

CONCLUSION The test substance is not inhibitory to algal growth.

TEST FACILITY IES (2017e)

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