File No: LTD/1993

October 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexadecanone

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Energy.

This Public Report is available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1993	Symrise Pty Ltd	Cyclohexadecanone	ND*	< 1 tonne per annum	Fragrance ingredient

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
As limited toxicity data were provided, the notified chemical cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

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 low toxicity to aquatic life and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- 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:
  - Avoid contact with eyes and skin

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Impervious gloves
  - Safety glasses

  Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  – the importation volume exceeds one tonne per annum notified chemical;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

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

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low volume permits

NOTIFICATION IN OTHER COUNTRIES
European Union (2008)

2. IDENTITY OF CHEMICAL

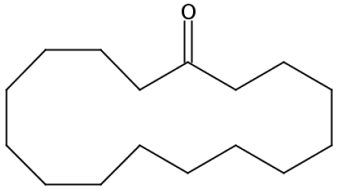
MARKETING NAME(S)
Isomuscone

CAS NUMBER
2550-52-9

CHEMICAL NAME
Cyclohexadecanone

MOLECULAR FORMULA
$C_{16}H_{30}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
238.41 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 98.5%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: pale white to white solid (scales)

Property	Value	Data Source/Justification
Melting Point/Freezing Point	67.4 °C at 102.1 kPa	Measured
Boiling Point	340.2 °C at 102.1 kPa	Measured
Density	923.6 ± 5.3 kg/m^3 at 20 °C	Measured
Vapour Pressure	7.3×10^{-5} kPa at 20 °C 1.6×10^{-4} kPa at 25 °C 5.6×10^{-3} kPa at 50 °C	Measured (extrapolated)
Water Solubility	0.13 mg/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Expected to be hydrolytically stable under environmental pH range (4-9) at ambient temperature
Partition Coefficient (n-octanol/water)	log P_{ow} = 7.77 at 25 °C	Measured
Adsorption/Desorption	log K_{oc} = 3.85-5.42 at 25 °C	Calculated by KOCWIN EPI Suite v4.11
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Not determined	Not imported in powder form
Flammability	Not low flammability (melts in contact with flame)	Measured
Autoignition Temperature	> 106°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 within Australia. The notified chemical will be primarily imported into Australia as a component of end-use cosmetic and household products at ≤ 3% concentration and to a lesser extent imported as a component of fragrance formulations at ≤ 20% concentration to be reformulated into end-use cosmetic and household products. Less frequently the notified chemical may also be imported as a component of fragrance formulations at ≤ 50% concentration or in the neat form for reformulation.

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
Throughout Australia

IDENTITY OF MANUFACTURER/RECIPIENTS
Symrise Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical may be imported as a component of fragrance formulations at ≤ 20% concentration in 30 L or 216 L closed lacquer-lined drums or in 30 L plastic canisters. If imported as the pure notified chemical it is expected to be packaged in dangerous goods cartons containing up to 15 kg each. Finished consumer products containing ≤ 3% notified chemical will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products (at ≤ 3% concentration in fine fragrances, at ≤ 0.35% concentration in other cosmetics and at ≤ 0.4% concentration in household products).

OPERATION DESCRIPTION
When not imported in end-use cosmetic and household products the notified chemical will be imported as a component of fragrance formulations at ≤ 20% concentration (less frequently at ≤ 100% concentration) for reformulation into cosmetic and household products.

Reformulation
The procedures for reformulating the fragrance formulations containing the notified chemical will likely vary depending on the nature of the cosmetic/household products, and may involve both automated and manual transfer steps. In general, it is expected that the reformulation processes will involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into consumer containers of various sizes.

End-use
The finished products containing the notified chemical (at ≤ 3% concentration in fine fragrances, at ≤ 0.35% concentration in other cosmetics and at ≤ 0.4% concentration in household products) may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the products, these could be applied in a number of ways, such as by hand, using an applicator or by spray.

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	unknown	unknown
Mixing	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	0.5	2
Packaging	4	2
Professional end users	1-8	200

EXPOSURE DETAILS
Transport and storage workers may come in contact with the notified chemical either at ≤ 20% concentration in fragrance formulations (less frequently at ≤ 100% concentration) or at ≤ 3% concentration in consumer products only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into consumer products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 20% concentration (less frequently at ≤ 100% concentration) may occur during weighing and addition of fragrance formulations containing the notified chemical to blending equipment, while testing for quality control and during equipment cleaning and maintenance. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End use
Exposure to the notified chemical in end-use products at ≤ 3% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hairdressers, 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 some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 3% concentration through the use of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure is 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 full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration assay	non genotoxic
Genotoxicity – in vitro gene mutation assay	non genotoxic

Toxicokinetics
Based on the low molecular weight (< 500 Da), there is potential for the chemical to cross biological membranes. However, this potential may be limited based on the water solubility (1.3×10^{-4} g/L at 20 °C) and partition coefficient (log Pow = 7.7 at 25 °C) of the notified chemical.

Acute toxicity
The notified chemical was found to be of low toxicity via the oral and dermal routes in studies conducted in rats. No acute inhalation toxicity data were submitted.

Irritation and sensitisation
In studies conducted in rabbits, the notified chemical was found to be non-irritating to the skin but slightly irritating to eyes. Eye irritation was limited to slight conjunctivae redness and chemosis which were fully resolved 48 hours after treatment.

No respiratory irritation data were submitted. Significant inhalation is not expected given the measured low vapour pressure (7.3×10^{-5} kPa at 20 °C) of the notified chemical.

Sensitisation
The notified chemical was not a skin sensitiser in guinea pigs when tested in a maximisation test (challenge by topical administration of 25% concentration).

Repeated dose toxicity
A repeated dose oral (gavage) toxicity study on the notified chemical was conducted in rats, in which the test substance was administered at 300, 600 and 1000 mg/kg bw/day for 28 consecutive days, with a 14-day recovery period for high dose and vehicle control animals.

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day (the highest dose tested) in the study, based on an absence of treatment-related adverse effects.

Mutagenicity/Genotoxicity
The notified chemical was negative in a bacterial reverse mutation assay, in an *in vitro* chromosome aberration test in Chinese hamster V79 cells and in an *in vitro* gene mutation assay.

Health hazard classification
As limited toxicity data were provided, the notified chemical cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available toxicological information the notified chemical is expected to be of low hazard to humans with the exception of being a mild eye irritant. Risks associated with inhalation toxicity (local or systemic) cannot be ruled out due to the absence of relevant data. Precautions are recommended to limit skin exposure to high concentrations of the notified chemical given the skin sensitisation test was conducted at only 25% concentration.

Reformulation
During reformulation, workers may be exposed to the notified chemical at up to 100% concentration. It is anticipated by the notifier that engineering controls such as enclosed and automated processes will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit worker exposure.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic and household products containing the notified chemical to clients (*e.g.*, hairdressers, beauty salon workers and cleaners) may be exposed to the notified chemical at concentrations up to 3%. 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
The public is likely to have repeated exposure to the notified chemical through use of cosmetic and household products containing it at ≤ 3% concentration. At the proposed use concentration, any potential for eye irritation is expected to be greatly reduced.

Therefore, the risk to the public from use of the notified chemical at ≤ 3% in fine fragrances, ≤ 0.35% in other cosmetics and ≤ 0.4% in household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be primarily imported into Australia as a component of end-use cosmetic and household products, and to a lesser extent 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. Wastewater from cleaning of the reformulation equipment, estimated by the notifier to contain up to 1% of the total annual import volume of the notified chemical, will be discharged to either onsite wastewater treatment plants or to sewers. Release of the notified chemical to the environment in the event of accidental spills or leaks during reformulation, storage and transport is expected to be absorbed on suitable materials and disposed of to landfill in accordance with local government regulations.

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

RELEASE OF CHEMICAL FROM DISPOSAL
It is expected that some products containing the notified chemical will remain in empty end-use containers. The residue of notified chemical in these empty containers are likely to either share the fate of the containers and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility. Empty import containers containing residue of the notified chemical will also be taken to an approved waste handling site for recycling or disposal.

7.1.2. Environmental Fate
Following its use in cosmetic formulations and household products, the majority of the notified chemical will enter the sewers and be treated at sewage treatment plants (STPs) before potential release to surface waters nationwide.

A ready biodegradation test for the notified chemical indicates that it is not readily biodegradable, but shows inherent biodegradability in aquatic environment (47% degradation over 28 days). For details of the biodegradation study, please refer to Appendix C. The notified chemical is expected to sorb to sludge at STPs based on its low water solubility (0.13 mg/L) and high partition coefficient (log P_{ow} = 7.77). Therefore, the notified chemical is expected to be removed effectively at STPs through biodegradation and adsorption to sludge, and only a small portion of the notified chemical may be released to surface waters. A proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation or disposed of to landfill. The notified chemical residues in landfill and soils are expected to have very low mobility based on its calculated soil adsorption coefficient (log K_{oc} = 3.85 - 5.42). The notified chemical is expected to have bioaccumulative potential based on the reported log P_{OW} of 7.77. However, this is not considered to be a concern since the notified chemical showed a biodegradability of 47% in 28 days. Additionally, the notified chemical is not expected to be significantly released to surface waters and is not harmful to aquatic life up to the limit of its water solubility. In the aquatic and soil compartments, the notified chemical is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The half-life of the notified chemical in air is calculated to be < 5 h, based on reactions with hydroxyl radicals (US EPA, 2011; calculated using AOPWIN v1.92). Therefore, the notified chemical is not expected to persist in the air 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 under the worst case scenario that 100% of the total import volume of the notified chemical is released to STPs and there is no removal of the notified chemical at STPs. The release is assumed to be nationwide over 365 days per year.

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	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.75 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 18.73 µg/kg and 37.45 µg/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 > 0.10 mg/L	Not harmful to fish up to its water solubility limit
Daphnia Toxicity	48 h EC50 > 0.19 mg/L	Not harmful to aquatic invertebrates up to its water solubility limit
Algal Toxicity	72 h EC50 > 0.18 mg/L	Not harmful to alga up to its water solubility limit
Inhibition of Bacterial Respiration	3 h IC50 > 5800 mg/L	Not harmful to activated sludge at STPs

The results from ecotoxicological investigations show that the notified chemical is not harmful to aquatic life up to its water solubility limit. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) for acute and chronic toxicities (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated as the notified chemical is not considered to be harmful to aquatic organisms.

7.3. Environmental Risk Assessment

The Risk Quotients (Q = PEC/PNEC) have not been calculated since the PNEC was not calculated. The notified chemical is not expected to be harmful to aquatic life. Therefore, based on the low toxicity to aquatic life 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 67.4 °C at 102.1 kPa

Method	Commission Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Determined using differential scanning calorimeter
Test Facility	Kesla (2001a)

Boiling Point 340.2 °C at 102.1 kPa

Method	Commission Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	Determined using differential scanning calorimeter
Test Facility	Kesla (2001b)

Density 923.6 ± 5.3 kg/m^3 at 20 °C

Method	Commission Directive 92/69/EEC A.3 Relative Density.
Remarks	Determined using pycnometer
Test Facility	Kesla (2001c)

Vapour Pressure 7.3×10^{-5} kPa at 20 °C
1.6×10^{-4} kPa at 25 °C
5.6×10^{-3} kPa at 50 °C

Method	Commission Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Static method Values extrapolated from measuments in the 43.1 – 68.5 °C range.
Test Facility	Siemens (2001)

Water Solubility 0.13 mg/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	Column Elution Method
Test Facility	IES (2016a)

Partition Coefficient (n-octanol/water) log Pow = 7.77 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water)
Remarks	HPLC Method
Test Facility	IES (2016b)

Flammability Not low flammability

Method	EC Directive 92/69/EEC A.10. Flammability (solids)
Remarks	The test substance melted and discoloured itself to white in contact with butane burner flame. A flammability test was not possible.
Test Facility	Kesla (2001d)

Autoignition Temperature No self-ignition at 29-106°C

Method	Commission Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks	The aimed investigated temperature range was from ambient to the melting point of 67.4 °C.
Test Facility	Kesla (2001e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Commission Directive 96/54/EEC B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.

Species/Strain	Rat/Wistar
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 per sex	2000	0/6

LD50	> 2000 mg/kg bw
Signs of Toxicity	No clinical signs of systemic toxicity were noted.
Effects in Organs	No macroscopic findings were noted at necropsy.
Remarks - Results	The body weight of the animals was within the range commonly recorded for this strain and age, with the exception of one female rat which had a reduced (26% of mean) body weight gain.

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

TEST FACILITY: Kesla (2001f)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: Commission Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.

Species/Strain	Rat/Wistar
Vehicle	Corn Oil
Type of dressing	Occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No signs of local toxicity were noted.
Signs of Toxicity - Systemic	No clinical signs of systemic toxicity were noted.
Effects in Organs	No macroscopic findings were noted at necropsy.
Remarks - Results	The body weight of the animals was within the range commonly recorded for this strain and age.

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

TEST FACILITY: Kesla (2001g)

B.3. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD	Commission Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	4
Vehicle	Ethanol/diethylphthalate (1:1)
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	No significant protocol deviations
Remarks - Results	No mortality or signs of systemic toxicity were noted. No irritation was noted in any skin area treated with the moistened test substance or with solutions of the test substance at 3 concentrations (10%, 25% and 50%).
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Kesla (2001h)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	Commission Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	4
Observation Period	72 hours
Remarks - Method	No significant protocol deviations Necropsy was not carried out due to the absence of clinical signs.

RESULTS

Lesion	*Mean Score**				*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4			
Conjunctiva: redness	0.3	0	0.3	0.3	1	< 48 h	0
Conjunctiva: chemosis	0.3	0	0.3	0	1	< 48 h	0
Corneal opacity	0	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	0	-	0

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

Remarks - Results	There were no mortalities or clinical signs observed. Slight conjunctivae redness and chemosis were noted in all animals at the 1-hour observation. Slight conjunctivae redness persisted in 3 animals and slight conjunctivae chemosis persisted in 2 animals at the 24-hour observation. The cornea and iris were not affected by treatment. All signs of irritation were resolved at the 48-hour observation.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Kesla (2001i)

B.5. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Commission Directive 96/54/EEC B.6 Skin Sensitisation – Magnusson-

	Kligman.
Species/Strain	Guinea pig/Dunkin Hartley, Crl:(HA)BR
PRELIMINARY STUDY	Maximum Non-irritating Concentration: topical: > 25%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 20
Vehicle	Arachis oil (intracutaneous administration) or ethanol/diethylphthalate (1:1) (epicutaneous administration)
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using benzocaine.
INDUCTION PHASE	Induction Concentration: intradermal: 5% topical: 25%
Signs of Irritation	Intracutaneous administration caused slight erythema and oedema. Pretreatment with sodium lauryl sulphate in Vaseline caused slight to moderate erythema in all animals on Day 7. Epicutaneous administration at the maximum concentration of 25% did not cause skin irritation.
CHALLENGE PHASE	
challenge	topical: 25%
Remarks - Method	No significant protocol deviations. As the test substance tested at 25% concentration (topical) did not cause irritation in a pilot study. A mild inflammatory response was induced by pre-treatment of the skin with 10% sodium lauryl sulphate in Vaseline 24 hours before topical induction.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*	
		48 h	*72 h*
Test Group	5%	0/20	0/20
Control Group (vehicle)	5%	0/10	0/10

Remarks - Results	No mortality or signs of systemic toxicity were noted. The mean body weight and body weight gain were not affected. No skin reactions were noted after the challenge.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Kesla (2001j)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	Commission Directive 96/54/EEC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/Wistar Crl:WI BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
water control	5 per sex	0	0/10
vehicle control	5 per sex	0	0/10
low dose	5 per sex	300	0/10
mid dose	5 per sex	600	0/10
high dose	5 per sex	1000	0/10
vehicle control recovery	5 per sex	0	0/10
high dose recovery	5 per sex	1000	0/10

Mortality and Time to Death

There were no mortalities during the treatment or recovery periods.

Clinical Observations

There were no treatment-related clinical signs.

Body weights, body weight gains and food consumption were not affected by the treatment. Isolated statistically significant differences between the treatment groups and the vehicle control group on body weight were considered by the study authors to be incidental.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology

No treatment-related effects on haematological parameters were noted.

Coagulation

Decreased prothrombin time was noted in female animals of all treatment dose groups but not dose-related. This effect was reversible during recovery.

Clinical Biochemistry

Increased serum cholesterol level was noted in all animals of all treatment dose groups and was irreversible in female animals during recovery.

Increased serum total protein and albumin levels were noted in female animals of the 600 and 1000 mg/kg bw/day dose groups and was reversible during recovery.

Effects in Organs

Organ Weight and Histology

Increased absolute and relative weights of the liver were noted in all treated animals and were irreversible in female animals during recovery. Increased liver weights were also noted in vehicle control group, compared to the water control group.

Intracellular vacuoles were noted in the hepatocytes of all animals in vehicle control and 1000 mg/kg bw/day dose groups without difference between the two groups but were not noted in the water control group. The study authors stated that these vacuoles were an indicator of fat deposits into the cells. Correlated effects such as an appearance of leucocytes, lymphocytes and a formation of cell detritus or microhaemorrhages as indications of cell damage were not noted. Therefore, the effect was considered by the study authors to be caused by the administration of the vehicle corn oil.

Macroscopic Pathology

No abnormalities were found.

Remarks – Results

The study authors stated that the effects on the liver were not strong and did not affect general wellbeing of the animals. All increased weights of the liver were in the range if the historical control data in the testing facility for the strain used. Macroscopic pathological effects were not noted, liver enzyme activities were not increased

and cell damage was not noted histologically.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the absence of test substance-related adverse effects at all doses tested.

TEST FACILITY Kesla (2001k)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD Commission Directive 92/69/EEC B.13 Mutagenicity (*Escherichia Coli* – Reverse Mutation Assay).
Commission Directive 92/69/EEC B.14 Mutagenicity (*Salmonella Typhimurium* – Reverse Mutation Assay).
Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from β-naphthoflavone/phenobarbitone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 10 - 1000 µg/plate b) Without metabolic activation: 10 - 1000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	A dose range-finding study was carried out at 10-5000 µg/plate. The dose selection for the main tests was based on precipitation observed in the range-finding study at 5000 µg/plate. The results of dose range-finding study were reported as part of Test 1 results.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 5000	> 1000	> 1000	negative
Test 2		> 1000	> 1000	negative
Present				
Test 1	≥ 5000	> 1000	> 1000	negative
Test 2		> 1000	> 1000	negative

Remarks - Results
No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

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

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

TEST FACILITY Kesla (2001l)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD EC Directive 92/69/EEC B.10 In Vitro Mammalian Cytogenetic Test

Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from β-naphthoflavone/sodium phenobarbitone induced rat liver

Vehicle	Dimethyl sulfoxide
Remarks - Method	A dose range-finding study was carried out at 8 – 500 µg/mL. The dose selection for the main experiments was based on toxicity observed in the range-finding study. Vehicle control and positive control (ethyl methanesulfonate and cyclophosphamide) were run concurrently with the notified chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	6*, 13*, 25*	4 h	18 h
Test 2	6*, 13*, 25*	18 h	18 h
Test 3	25*	26 h	26 h
Present			
Test 1	13*, 25*, 50*	4 h	18 h
Test 2	13*, 25*, 50*	4 h	18 h
Test 3	50*	4 h	26 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 30	≥ 25	> 25	negative
Test 2		≥ 25	> 25	negative
		≥ 25	> 25	negative
Present				
Test 1	≥ 30	≥ 50	> 50	negative
Test 2		≥ 50	> 50	negative
Test 3		≥ 13	> 25	negative

Remarks - Results	In both main tests, no statistically significant increases in the frequency of cells with structural or numerical chromosome aberrations were observed in the presence or absence of metabolic activation. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test.
TEST FACILITY	Kesla (2001m)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.
Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Ethanol
Remarks - Method	The first dose range-finding study was carried out at 15.6 – 2000 µg/mL, which was not analysable in the absence of metabolic activation following 4 hours due to severe cytotoxicity. Therefore, a second dose range-finding study was carried out at 0.13 – 16 µg/mL without metabolic activation (reported as Test 1 without metabolic activation). The dose selection for

the main experiments was based on toxicity observed in the range-finding studies.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0.5, 1*, 2*, 4*, 6*, 8*, 12, 16	4 h	7 days	8 days
Present				
Test 1	2, 4*, 8*, 16*, 32*, 48, 64	4 h	7 days	8 days
Test 2	16, 32*, 36*, 40*, 44*, 48*	4 h	7 days	8 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	≥ 15.6	≥ 6	> 16*	negative
Test 2	≥ 2			
Present				
Test 1	≥ 62.5	> 64	> 64*	negative
Test 2		> 48	> 48*	negative

* Precipitation was observed at ≥ 250 µg/mL in the absence/presence of metabolic activation in the first dose range-finding study.

Remarks - Results

In both main tests, no substantial and reproducible dose-dependent increases in the frequency of revertant colonies were observed in the presence or absence of metabolic activation.

The positive control and vehicle control gave a satisfactory response confirming the validity of the test system.

CONCLUSION

The notified chemical was not clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test.

TEST FACILITY

Envigo (2017)

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
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical oxygen demand (ThOD)
Remarks - Method	No significant deviations from the test guidelines were reported. The reference item was prepared from a concentrated stock and inoculated mineral medium. Due to low solubility of the test item, a concentrated stock could not be prepared so the test item was directly weighted and stirred in the test flasks.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*[*]	*Day*	*% Degradation*[*]
4	11	4	78
7	23	7	85
11	35	11	89
14	38	14	92
21	43	21	93
28	47	28	95

[*]Mean value of two replicates

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 60 % within 14 days indicating the suitability of the inoculums. The toxicity control exceeded 25% biodegradation after14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 47%.
CONCLUSION	The notified chemical is not readily biodegradable, but shows inherent biodegradability
TEST FACILITY	IES (2016c)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test –Semi Static. EE Directive 92/69/EEC Method C.1 Acute Toxicity for Fish – Semi Static.
Species	*Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	40-180 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography-flame ionisation detector (GC-FID)
Remarks – Method	No significant deviations from the test guidelines were reported. The test

substance was weighted and mixed with the test medium. The suspension was filtered (0.45 µm) prior to introduction of test organisms.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
0.10	0.10	7	0	0	0	0	0

LC50	> 0.1 mg/L at 96 hours
NOEC	0.1 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied

CONCLUSION The notified chemical is not harmful to fish up to its water solubility limit

TEST FACILITY Dr U Noack Laboratorium (2001a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.
EC Directive 92/69/EEC Method C.2 Acute Toxicity for Daphnia – Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	160-180 mg $CaCO_3$/L
Analytical Monitoring	GC-FID
Remarks - Method	No significant deviations from the test guidelines were reported. The saturated stock solution was stirred 24 hours and filtered (0.45 µm) prior to introduction of test organisms.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
0.19	0.19	20	0	0

LC50	> 0.19 mg/L at 48 hours
NOEC	0.19 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied

CONCLUSION The notified chemical is not harmful to aquatic invertebrates up to its water solubility limit

TEST FACILITY Dr U Noack Laboratorium (2001b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
EC Directive 92/69/EEC Method C.3 Algal Inhibition Test.

Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0, 0.18 mg/L Actual: 0, 0.18 mg/L
Auxiliary Solvent	None

Water Hardness	Not determined
Analytical Monitoring	GC-FID
Remarks - Method	No significant deviations from the test guidelines were reported. The saturated stock solution was filtered through membrane before use.

RESULTS

Biomass		*Growth*	
EC50 mg/L at 72h	*NOEC mg/L*	*EC50 mg/L at 72 h*	*NOEC mg/L*
> 0.18	≥ 0.18	> 0.18	≥ 0.18

Remarks - Results	All validity criteria for the test were satisfied

CONCLUSION The notified chemical is not harmful to alga up to its water solubility limit

TEST FACILITY Dr U Noack Laboratorium (2001c)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated sludge at a local STP
Exposure Period	3 hours
Concentration Range	Nominal: 0, 1000, 1800, 3200, 5800, 10000 mg/L Actual: Not determined
Remarks – Method	No significant deviations from the test guidelines were reported. The test item was concentration related partially dispersed.

RESULTS

IC50	> 5800 mg/L
Remarks – Results	All validity criteria for the test were satisfied

CONCLUSION The notified chemical is not harmful to activated sludge at STPs

TEST FACILITY Dr U Noack Laboratorium (2001d)

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