File No: STD/1572

May 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Propanoic acid, 2-hydroxy, 2-(C_{10-16}-alkyloxy)-1-methyl-2-oxoethyl ester (INCI Name: Lauryl Lactyl Lactate)

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.

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/1572	IXOM Operations Pty Ltd	Propanoic acid, 2-hydroxy, 2-(C_{10-16}-alkyloxy)-1-methyl-2-oxoethyl ester (INCI Name: Lauryl Lactyl Lactate)	No	≤ 75 tonnes per annum	Cosmetic ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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 assessed 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 as introduced:
  – Avoid eye contact

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

- A copy of the (M)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.

Public Health

- Product formulators should exercise due care when using the notified chemical in cosmetic products given its potential ability to enhance the dermal penetration of other chemicals in the formulation.

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, 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 notified chemical is proposed to be used in cosmetic products at a concentration exceeding 1%;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a cosmetic 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.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
IXOM Operations Pty Ltd (ABN: 51 600 546 512)
Level 8
1 Nicholson Street
EAST MELBOURNE VIC 3002

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: other names, analytical data, degree of purity, residual monomers, impurities, use details, and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: partition coefficient, adsorption/desorption and acute dermal toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
United States of America (2008)
Canada (2009)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
STEPAN-MILD® L3

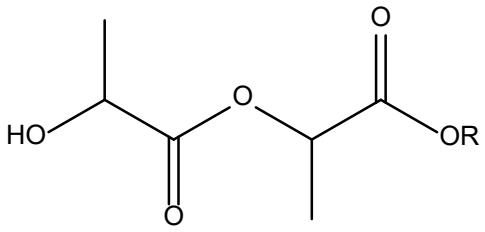
CAS NUMBER
910661-93-7

CHEMICAL NAME
Propanoic acid, 2-hydroxy, 2-(C_{10-16}-alkyloxy)-1-methyl-2-oxoethyl ester

OTHER NAME(S)
Lauryl Lactyl Lactate (INCI Name)

MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA



where R = C_{10} - C_{16} (predominantly C_{12})

MOLECULAR WEIGHT
302.4 – 386.6 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 80%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless liquid

Property	Value	Data Source/Justification
Melting Point	-11.15 °C	Measured
Boiling Point	312.1 °C at 98.5 kPa	Measured
Density	972 kg/m^3 at 20 °C	Measured
Vapour Pressure	0.032 kPa at 20 °C	Measured
Water Solubility	< 3× 10^{-4} g/L at 20 °C	Measured. Based on its structure, the notified chemical is expected to have low water solubility and be surface active.
Hydrolysis as a Function of pH	100 mg/L solution stable at pH 7 for > 96 hrs	Measured. The notified chemical contains hydrolysable functionalities, however, hydrolysis is expected to be slow under environmental conditions (pH 4 – 9).
Partition Coefficient (n-octanol/water)	log Pow = 4.69 at 20 °C	Estimated using US EPA EPI Suite™ v.3.20, KOWWIN v.1.67. Based on the structure and its use, the notified chemical is expected to be a non-ionic surfactant and hence an accurate measure of its partition coefficient cannot be obtained.
Adsorption/Desorption	log K_{oc} = 2.3	Estimated US EPA EPI Suite™ v EPIWIN WSKOW v.1.41. The notified chemical is expected to be a non-ionic surfactant and hence an accurate measure of its adsorption coefficient cannot be obtained.
Dissociation Constant	Not determined	The notified chemical does not contain any functional groups that are expected to dissociate in water.
Flash Point	169 °C	Measured
Autoignition Temperature	365 °C	Measured
Explosive Properties	Not determined	Not expected to be explosive based on structure
Oxidising Properties	Not determined	Not expected to be oxidising based on structure

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia in its pure form (> 80% concentration) for reformulation.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	10 – 30	10 – 30	30 – 60	30 – 60	50 - 75

PORT OF ENTRY
Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
IXOM Operations Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical (at > 80% concentration) will be imported into Australia in 200 L metal drums. The notified chemical will be transported from port of entry by road to the notifier's warehouse facilities for storage in its original packaging until transportation to the customer site. End-use products (containing the notified chemical at ≤ 1% concentration) will be packaged in typical consumer-sized containers suitable for retail sale.

USE
The notified chemical will be used as a surfactant in a variety of cosmetic products at ≤ 1% concentration.

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging will occur at the notifier's facility. The imported products containing the notified chemical (at > 80% concentration) will be stored at the notifier's facilities until they are transported to customer facilities (in original importation packaging).

At the customer facilities, the procedures for incorporating the notified chemical (at > 80% concentration) into end-use products will likely vary depending on the nature of the cosmetic products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed environment followed by automated filling of the reformulated products into containers of various sizes.

End-use products
Cosmetic products containing the notified chemical (at ≤ 1% concentration) may be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand or the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and Storage workers	unspecified	unspecified
Reformulation/QC	< 1	55
End users	unspecified	unspecified

Exposure Details
Transport and storage
Transport and storage workers may come into contact with the notified chemical in its pure form or in end-use products (≤ 1% concentration), only in the event of accidental rupture of containers.

Reformulation
During reformulation, dermal and ocular exposure of workers to the notified chemical (in pure form) may occur during weighing and transfer stages, equipment preparation, blending, quality control analysis, and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of automated/enclosed systems and personal protective equipment (PPE) such as gloves, eye protection, and coveralls.

End-use
Exposure to the notified chemical in end-use products (at ≤ 1% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hairdressers, workers in beauty salons). Such professionals may use 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 ≤ 1% concentration) through the use of both rinse-off and leave-on cosmetic products. The principal route of exposure will be dermal, while accidental ocular and oral exposure (from the use of lip products) is also possible.

A combined internal dose of 2.2149 mg/kg bw/day was estimated using data on typical use patterns of cosmetic product categories in which the notified chemical may be used (SCCS, 2012; specific use details of the notified chemical are considered as exempt information). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic products that may contain the notified chemical.

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 > 5,000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Human, skin sensitisation – RIPT (10%)	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 vivo mammalian micronucleus test	non genotoxic

Toxicokinetics.
No information on the toxicokinetics of the notified chemical was provided. The notified chemical is of low water solubility (< 3×10^{-4} g/L at 20 °C) and is surface active, therefore dermal absorption is expected to be limited. However the notified chemical may have the ability to enhance dermal penetration of other chemicals in the formulations.

Acute toxicity.
The notified chemical was found to be of low acute oral toxicity in rats. No acute dermal toxicity data was provided. The notified chemical has been found of low acute and systemic oral toxicity, and dermal absorption is expected to be limited. The notified chemical is therefore expected to be of low acute dermal toxicity.

Irritation.
In studies conducted in rabbits, the notified chemical was found to be non-irritating to the skin and slightly irritating to the eye.

Sensitisation.
The notified chemical showed no evidence of reactions indicative of skin sensitisation in a LLNA study on mice. In a human repeat insult patch test (HRIPT; 53 subjects completed the study), the notified chemical (at 10% concentration) was not considered by the study authors to induce skin sensitisation.

Repeated dose toxicity.
In a 28 day repeat dose study by oral gavage, rats were administered the notified chemical at doses of 30, 300 or 1000 mg/kg bw/day. The study authors concluded that the centrilobular hepatocellular hypertrophy observed in animals in the mid- (1 male, 1 female) and high-dose (all animals) groups were indicative of an adaptive response by the liver as no other associated inflammatory or degenerative changes were recorded. Centrilobular hepatocellular hypertrophy has been observed in rodent livers following treatment with xenobiotics and is associated with induction of microsomal enzymes. The effects noted for animals in the mid- and high- dose group were not considered by the study authors to be toxicologically significant. Therefore, the No Observed Adverse Effect Level (NOAEL) was established by the study authors as 1,000 mg/kg bw/day.

Mutagenicity/Genotoxicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study and non-clastogenic in an *in vivo* mammalian micronucleus test.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is of low hazard presenting only as a slight eye irritant.

Reformulation
During reformulation workers may be at risk of slight eye irritation effects when handling the notified chemical as introduced at > 80% concentration. However, this risk should be reduced through the control measures in place to minimise worker exposure, including the use of automated processes and PPE. Therefore, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use
Beauty care professionals will handle the notified chemical at ≤ 1% concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health
Irritation
The notified chemical has the potential to cause slight eye irritation. However, eye irritation effects are not expected from use of the notified chemical at the proposed concentrations (≤ 1%) in cosmetic products.

Repeated dose toxicity
Members of the public may experience repeated exposure to the notified chemical through the use of the cosmetic products (containing the notified chemical at ≤ 1% concentration).

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 2.2149 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 1000 mg/kg bw/day, as determined by the study authors in a 28-day repeated dose toxicity study on the notified chemical. Using the abovementioned NOAEL, a MoE of 472 was estimated. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure; therefore, the MoE is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 1% concentration in cosmetic 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 not be manufactured in Australia; therefore there is no release of the notified chemical to the environment from this activity. 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 notified chemical will be blended with other ingredients in automated/enclosed facilities to produce personal care products. Release from blending is expected to be very low. A total of up to < 1% of the import volume is estimated to be generated as waste from residues in empty containers and spills during blending. Empty containers containing the notified chemical will either be recycled or disposed of through an approved waste management facility.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic products, which are washed off the hair and skin of consumers and disposed of to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. The containers are expected to be disposed of through domestic garbage disposal and will enter landfill, or be subjected to recycling processes.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. The biodegradation study indicated that the notified chemical is considered to be readily degradable (78.9% after 28 days) in the environment and hence, it is expected to be degraded during the wastewater treatment process. Based on its estimated low adsorption coefficient value, only limited partitioning to sludge is expected. The notified chemical may bioaccumulate based on its low molecular weight. However, this potential to be accumulative is expected to be significantly reduced by the ready biodegradability. Further, the notified chemical is not expected to be bioavailable due to its limited water solubility. In surface waters, the notified chemical is expected to 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 6.612 hours based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have moderate mobility based on its low soil adsorption coefficient. In the aquatic and soil compartments, the notified chemical is expected to degrade through biotic and abiotic processes to form water and oxides of carbon.

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 cosmetic 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. For the calculation, 79% mitigation is estimated as the notified chemical would be degraded during sewage treatment.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	75,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	75,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	205.48	kg/day

Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	79%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	9.54	µg/L
PEC - Ocean:	0.95	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 9.541 µg/L may potentially result in a soil concentration of approximately 63.61 µg/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 0.318 mg/kg and 0.636 mg/kg, respectively.

7.2. Environmental Effects Assessment

Ecotoxicological data were submitted for the notified chemical. Details of the studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity (96 h)	EC50 > 100 mg/L	Not harmful up to the limit of solubility
Daphnia Toxicity (48 h)	EC50 = 0.58 mg/L	Not harmful up to the limit of solubility
	NOEC = 0.38 mg/L	Not harmful up to the limit of solubility
Algal Toxicity (72 h)	E_rC50 = 0.61 mg/L	Not harmful up to the limit of solubility
	NOEC = 0.09 mg/L	Not harmful up to the limit of solubility

Classification should be based only on toxic responses observed in the soluble range. The ecotoxicity endpoints for the notified chemical are higher than its solubility limit. It is concluded that the notified chemical is not expected to be harmful to organisms in either the aquatic or soil compartments up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic effects.

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) for the aquatic compartment has not been calculated since the notified chemical is not considered to be harmful up to the limit of its solubility in water.

7.3. Environmental Risk Assessment

The Risk Quotient (RQ = PEC/PNEC) has not been calculated since the PEC and PNEC were not calculated. The notified chemical is not harmful up to the limit of its solubility in water and is not expected to bioaccumulate in the environment. Therefore, based on the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk of the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point -11.15 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Differential Scanning Calorimetry. The freezing Point was measured as -13.99 °C
Test Facility	Stepan (2008)

Boiling Point 312.1 °C at 98.5 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Capillary method.
Test Facility	CiTox (2015a)

Density 972 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	Oscillating U-tube method
Test Facility	CiTox (2015b)

Vapour Pressure 0.032 kPa at 20 °C

Method	EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Static method using a U-tube manometer
Test Facility	Chilworth (2015)

Water Solubility $< 3 \times 10^{-4}$ g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Column Elution Method. The result was that the solubility of test item is lower than the limit of the quantitation of the method < 300 ng/mL) in HPLC water.
Test Facility	CiTox (2015c)

Hydrolysis as a Function of pH Stable at pH 7 for > 96 hrs

Method	Stepan Company internal method.
Remarks	100 mg/L solution was stable at pH 7 for > 96 hrs. Stability of the notified chemical at concentrations of 10 mg/L could not be determined because of the limit of detection.
Test Facility	Stepan Company (2009)

Flash Point 169 °C

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method.
Test Facility	CiTox (2015c)

Autoignition Temperature 365 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	CiTox (2015d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Sprague-Dawley
- Vehicle: None
- Remarks - Method: No protocol deviations. GLP compliant.

RESULTS

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

- LD50: > 5,000 mg/kg bw
- Signs of Toxicity: No adverse clinical effects noted.
- Effects in Organs: No abnormalities observed.
- Remarks - Results: All animals exhibited satisfactory body weight gains.

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

TEST FACILITY: Tox Monitor (2007a)

B.2. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 3 F
- Vehicle: None
- Observation Period: 72 hours
- Type of Dressing: Semi-occlusive.
- Remarks - Method: No protocol deviations. GLP compliant.

RESULTS

- Remarks - Results: No skin irritation reactions were observed in any of the animals. No significant body weight changes were observed over the 72 hr test period.

CONCLUSION: The notified chemical is non-irritating to the skin.

TEST FACILITY: Tox Monitor (2007b)

B.3. Irritation – eye

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rabbit/New Zealand White
- Number of Animals: 3 F
- Observation Period: 72 hours
- Remarks - Method: No protocol deviations. GLP compliant

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	0.3	0	0.3	1	< 48 hours	0
Conjunctiva: chemosis	0	0	0	0	< 24 hours	0
Conjunctiva: discharge	0	0	0.3	1	< 48 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results

All animals exhibited slight chemosis and discharge of the conjunctiva 1 hour post-exposure. Slight discharge persisted in one animal to the 24 hour observation. Full recovery from chemosis was observed in all animals at the 24 hour observation and no animals exhibited conjunctival discharge at the 48 hour observation.

Slight (2/3 animals) to moderate (1/3 animals) conjunctival redness was observed 1 hour post exposure. Slight conjunctival redness persisted in two animals 24 hours post exposure with recovery in all animals 48 hours post exposure.

No adverse corneal opacity or iridial inflammation was observed in any of the animals following exposure.

No significant body weight changes were observed over the 72 hr test period.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Tox Monitor (2007c)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain: Mouse/CBA/CaOlaHsd

Vehicle: Propylene glycol

Preliminary study: Yes

Positive control: 25% α-Hexyl cinnamaldehyde (HCA)

Remarks - Method

Preliminary test was performed at 50% and 100% concentration. No mortalities were observed. Adverse clinical effects were observed in animals exposed to the undiluted tests substance including hunched back, piloerection and decreased activity. Erythema (on ears and top of head) was also observed. Significant increases in ear thickness (≥ 25%) were observed in animals exposed to undiluted test substance (100%). Strong local irritation was observed in animals exposed to the test substance at 50% concentration.

An additional 6 animals were tested with 5%, 10% and 25% concentrations of the test substance (2 animals per dose). No mortalities were observed. No erythema was observed. Slightly increased ear thickness values were recorded, but these were within acceptable ranges.

^{3}H-methyl thymide (^{3}HTdR) was used to visualise the lymph node cells.

No protocol deviations.

GLP compliant.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4 F	378.9 (± 105.3)	1.0
5	4 F	379.3 (± 105.3)	1.0
10	4 F	461.8 (± 189.9)	1.2
25	4 F	818.8 (± 214.5)	2.2
Positive Control			
25% HCA	4 F	3719.6 (± 1361.3)	9.8

Remarks - Results

No mortalities or signs of systemic toxicity were noted in the test or control animals. No signs of local skin irritation (erythema) were observed.

Positive and negative controls performed as expected.

CONCLUSION

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

TEST FACILITY

CiTox (2015f)

B.5. Skin sensitisation – human volunteers

TEST SUBSTANCE

Test substance (10% concentration)

METHOD

Repeated insult patch test with challenge

Study Design

Induction Procedure: Patches containing 0.05 mL test substance were applied at 48 – 72 h intervals for a total of 9 applications. Patches were removed by the applicants after 48 h (or 2 h prior to study visit) and sites were graded 48 – 72 h after each application.
Rest Period: 12 - 24 days
Challenge Procedure: A patch was applied to the original and a naïve site. Patches were removed by the applicants after 48 h (or 2 h prior to challenge visit). Sites were graded 48 and 96 h post-application.

Study Group

53 F; age range 20.57 – 62.8 years

Vehicle

Olive Oil

Remarks - Method

Occluded. Patch size not reported.

A positive control was not used based on concerns for excessive skin irritation potential and subsequent hyper-pigmentation in subjects of North-East Asian origin. Historical positive control data was available.

RESULTS

Remarks - Results

All 53 subjects completed the study. Two subjects voluntarily withdrew prior to the study commencing (original study size of 55 subjects).

Mild (1/53 subjects, induction observations 2, 6, 8, 9), moderate (1/53 subjects, induction observations 1, 2) and severe (1/53 subjects, induction observations 3, 4, 5, 6, 7, 8, 9) erythema was observed. All other subjects exhibited no adverse effect.

At challenge, mild erythema was observed in 1/53 subjects at the original test site 48 h and 96 h post-application and in 1/53 subjects at the naïve site 96 h post-application. No other adverse responses were noted at challenge.

	The negative control performed as expected. Individual data for each test subject was not provided.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	Stephens (2009)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Wistar Han™:RccHan™:WIST
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	Arachis oil BP
Remarks - Method	GLP compliant. No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 M, 5 F	0	0/10
low dose	5 M, 5 F	30	0/10
mid dose	5 M, 5 F	300	0/10
high dose	5 M, 5 F	1000	0/10
control recovery	5 M, 5 F	0	0/10
high dose recovery	5 M, 5 F	1000	0/10

Mortality and Time to Death
No deaths were recorded in the study.

Clinical Observations
Intermittent episodes of increased salivation were observed at time of dosing in both sexes in the high dose group (between days 7 and 26) and one female in the mid-dose group (day 18). No other treatment related clinical effects were observed. All animals made the expected amount of body weight gains.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No statistically significant changes in the haematology, blood chemistry or urinalysis were observed. Any changes observed were considered to be incidental and not biologically relevant by the study authors.

Effects in Organs
One male in the low-dose group exhibited increased pelvic space in the right kidneys. However no other abnormalities in the remaining tissues were observed. This change was considered to be incidental and unrelated to exposure to the test substance by the study authors. No other macroscopic abnormalities were recorded in any of the other control animals or those exposed to the test substance.

Liver and spleen weights in low- and high-dose males and increased spleen weight in high-dose recovery male not considered toxicologically important by the study authors.

Centrilobular hepatocellular hypertrophy at minor severity degrees was observed in 1 male and 1 female in the mid-dose group and all animals in the high-dose group. The study authors indicated that this effect is seen in rodent livers following treatment with xenobiotics and is associated with induction of microsomal enzymes. Based on the absence of the effect in animals in the high-dose recovery group and the absence of associated inflammatory or degenerative changes, the study authors considered the effect to be an adaptive response by the

liver.

Remarks – Results
Based on the results of this study, 30 mg/kg bw/day was established as the no observed effect level (NOEL), whereas 1000 mg/kg bw/day was considered to be the no observed adverse effect level (NOAEL) as the observed changes were considered to be an adaptive response rather than an indication of systemic toxicity

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on absence of adverse effects at all doses tested.

TEST FACILITY Harlan (2013)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA

Metabolic Activation System S9 fraction from phenobarbital/β-naphthoflavone induced rat liver.

Concentration Range in Main Test Test 1:
TA100, WP2uvrA (also formed the dose-range study)
a) With metabolic activation: 3 - 5000 µg/plate
b) Without metabolic activation: 3 – 5000 µg/plate
TA1535, TA1537, TA98
a) With metabolic activation: 3 - 1000 µg/plate
b) Without metabolic activation: 3 – 1000 µg/plate

Test 2:
TA1535, TA1537, TA98, WP2uvrA
a) With metabolic activation: 10 - 1000 µg/plate
b) Without metabolic activation: 10 – 1000 µg/plate
TA100
a) With metabolic activation: 3 - 666 µg/plate
b) Without metabolic activation: 3 – 666 µg/plate

Vehicle Dimethylsulfoxide

Remarks - Method GLP compliant.
No significant protocol deviations.

A 5% (v/v) S9-mix was used in the dose-range study and Test 1 and a 10% (v/v) S9-mix was used in Test 2.

Positive controls (without metabolic activation): Sodium azide (TA1535), 9-Aminoacridine (TA1537), 2-Nitrofluorene (TA98), methylmethanesulfonate (TA100), 4-Nitroquinoline N-oxide (WP2uvrA); (with metabolic activation): 2- Aminoanthracene.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 1000	≥ 100	≥ 1000	negative
Test 2		≥ 100	≥ 1000	negative
Present				
Test 1	≥ 1000	≥ 1000	≥ 1000	negative

Test 2	≥ 100	≥ 666	negative

Remarks - Results	In the dose range study component of test 1, no toxicity was observed in WP2uvrA in the presence or absence of metabolic activation. Toxicity was observed in TA100 from 100 µg/plate in the absence of metabolic activation and from 1000 µg/plate in the presence of metabolic activation. Toxicity was observed in TA1535 in the absence and presence of metabolic activation [at 5% (v/v)] from 1000 µg/plate and from 100 µg/plate in TA1537 in the absence of metabolic activation in test 1. In test 2, toxicity was observed in TA1535 in the absence of metabolic activation from 333 µg/plate and from 100 µg/plate in TA1537 and TA100 in the absence and presence of metabolic activation at 10% (v/v). No biologically significant increase in the number of revertant colonies was observed in any of the tester strains examined in the absence and presence of metabolic activation in any of the tests conducted. Negative and positive controls performed as expected.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	NOTOX (2007)

B.8. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/ Hsd: ICR (CD-1®)
Route of Administration	Intraperitoneal injection
Vehicle	Arachis oil
Remarks - Method	GLP compliant. No significant protocol deviations. A preliminary toxicity test of 1000 mg/kg bw (1 M, 1 F) and 2000 mg/kg bw (3 M, 3 F) was performed with no observable clinical signs of toxicity after dosing. Male animals were chosen for the main test as no marked differences in toxicity was observed between the sexes. Animals were dosed once in the preliminary and main studies. Two groups of mice (group IV and V) were exposed to the highest dose (2000 mg/kg bw) and sacrificed at 24 hr and 48 hr respectively. Vehicle and positive controls were run concurrently.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	7 M	0	24
II (low dose)	7 M	500	24
III (mid dose)	7 M	1000	24
IV (high dose)	7 M	2000	24
V (high dose)	7 M	2000	48
V (positive control, CP)	5 M	50	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	Signs of toxicity were not observed at any dose level.
Genotoxic Effects	Systemic absorption of the test substance eliciting a bone marrow response was indicated in all groups exposed to the test substance (statistically significant decrease in animals in the low-dose group). No statistically significant increase in the number of micronucleated polychromatic erythrocytes was observed.
Remarks - Results	No mortalities were observed No substantial increase in the incidence of micronucleated normochromatic erythrocytes or significant decrease in the proportion of polychromatic erythrocytes was observed. Positive and negative controls performed as expected.

CONCLUSION The notified chemical was not clastogenic under the conditions of this in vivo mammalian micronucleus test.

TEST FACILITY Harlan (2010)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.

Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None Reported
Analytical Monitoring	Dissolved Organic Carbon (DOC)
Remarks - Method	The test was conducted in accordance with the test guideline above with no significant deviation from the protocol reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	25.23	4	56.34
7	50.93	7	80.07
10	60.44	14	86.54
24	77.19	21	84.33
29	78.92	28	77.20

Remarks - Results: The cumulative net CO_2, evolved from the sodium benzoate procedural control was 86.5% of theoretical by day 10, thus exceeding the "pass" criteria of the test. This rapid biodegradation of sodium benzoate confirmed the presence of an active microbial population and system integrity. The notified chemical showed 78.9% degradation in 28 days meeting the 10-day window criterion.

CONCLUSION: The notified chemical is readily biodegradable.

TEST FACILITY: Springborn Smithers Laboratories (2007)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test - Static.

Species	Fathead Minnow *(Pimephales promelas)*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	132 mg $CaCO_3$/L
Analytical Monitoring	High performance liquid chromatography (HPLC)
Remarks – Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. Primary stock solution was prepared in dimethylformamide (DMF) which was then diluted to prepare relevant concentrations.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*				
Nominal		*5.5h*	*24 h*	*48 h*	*72 h*	*96 h*
6.3	10	0	0	0	0	0
13	10	0	0	0	0	0
25	10	0	0	0	0	0
50	10	0	0	0	0	0
100	10	0	0	0	0	0

LC50	> 100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	All validity criteria were within acceptable limits.

CONCLUSION	The notified chemical is not harmful to fish
TEST FACILITY	Wildlife (2007a)

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
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	134 mg $CaCO_3$/L
Analytical Monitoring	High performance liquid chromatography using (HPLC)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. Primary stock solution was prepared in DMF which was then diluted with water to prepare relevant concentrations. All test solutions appeared clear and colourless at test termination.

RESULTS

Concentration mg/L	*Number of D. magna*	*Number Immobilised*	
Nominal		*24 h*	*48 h*
0.38	10	0	0
0.75	10	0	8
1.5	10	5	10
3.0	10	7	10
6.0	10	9	10
12.0	10	6	10

LC50	0.58 mg/L at 48 hours
NOEC	0.38 mg/L at 48 hours
Remarks - Results	The 48-hour EC50 value was 0.58 mg/L, with 95% confidence limits of 0.38 and 0.75 mg/L. Based on the mortality and immobility observed in the 0.75 mg/L treatment group, the NOEC was considered to be 0.38 mg/L..
CONCLUSION	The ecotoxicity endpoints for the notified chemical are higher than its solubility limit. Therefore, the notified chemical is not harmful to daphnia up to the limit of its water solubility
TEST FACILITY	Wildlife International Ltd (2007)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	96 hours
Concentration Range	Nominal: 0.0081,0.027,0.090,0.3 and l.0 mg/L
Auxiliary Solvent	None reported
Water Hardness	None reported
Analytical Monitoring	High performance liquid chromatography (HPLC)
Remarks - Method	The primary stock solution at a nominal concentration of 10 mg/mL was prepared by dissolving 0.10 g of the notified chemical in 10 mL of DMF which was then diluted with water to prepare relevant concentrations. The primary stock and each of the prepared test solutions were clear and colourless.

RESULTS

	Biomass		*Growth*	
	E_yC50 mg/L	*NOEC mg/L*	*E_yC50 mg/L at*	*NOEC mg/L at*
72 h	0.20 - 0.34	0.090	0.56 - 0.66	0.090
96 h	0.68 - 0.70	0.30	> 1.0	0.30

Remarks - Results	The 72-hour values for cell density and growth rate were 0.26 and 0.61 mg/L, respectively. The 96-hour values for cell density and growth rate were 0.69 and >1.0 mg/L, respectively. At 72 hours, the NOEC for cell density, biomass and growth rate were all 0.090 mg/L.. The 96-hour NOAEC for biomass was 0.090 mg/L. However, the classification should be based only on toxic responses observed in the soluble range.
CONCLUSION	The ecotoxicity endpoints for the notified chemical are higher than its solubility limit in water. Therefore, the notified chemical is not harmful to algae up to the limit of its water solubility
TEST FACILITY	Wildlife International Ltd (2007)

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