File No: STD/1471

February 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tri-C_{14-15}-alkyl esters (INCI name: Tri-C14-15 alkyl citrate)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (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.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This Public Report is also 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/1471	L'Oreal Australia Pty Ltd	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tri-C_{14-15}-alkyl esters (INCI name: Tri-C14-15 Alkyl Citrate)	No	3 tonnes per annum	Ingredient in cosmetics

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 for the 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 expected 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 engineering controls to minimise occupational exposure to the notified chemical:
  - Closed systems for blending, when available

- 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 formulation:
  - Goggles
  - Coveralls
  - Impervious gloves
  - Respiratory protection if ventilation is inadequate

  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.

Disposal

- The notified chemical should be disposed of to landfill.

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 concentration of the notified chemical is intended to exceed 10% as an ingredient in cosmetics;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from ingredient in cosmetics, 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 and products containing the notified chemical provided by the notifier were 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)
L'Oreal Australia Pty Ltd (ABN: 40 004 191 673)
564 St Kilda Road
Melbourne VIC 3004

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Details of some study reports.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: all physico-chemical properties, acute inhalation toxicity, some genotoxicity endpoints, repeated dose toxicity, bioaccumulation, fish acute toxicity, acute immobilisation test, algal growth inhibition test and ready biodegradability test.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)

None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Tri-C14-15 alkyl citrate

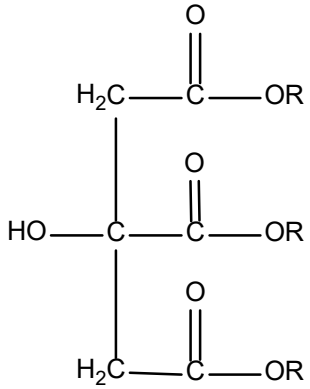
CAS NUMBER
222721-94-0

CHEMICAL NAME
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tri-C_{14-15}-alkyl esters

OTHER NAME(S)
Tri-C14-15 Alkyl Citrate (INCI name)

MOLECULAR FORMULA
$C_{48}H_{92}O_7$ to $C_{51}H_{98}O_7$

STRUCTURAL FORMULA



R = C14-C15 alkyl group

MOLECULAR WEIGHT
781-823 Da

ANALYTICAL DATA
IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY
90-95 %

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None known.

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

Chemical Name	C14-15 Alcohols		
CAS No.	75782-87-5	*Weight %*	5%

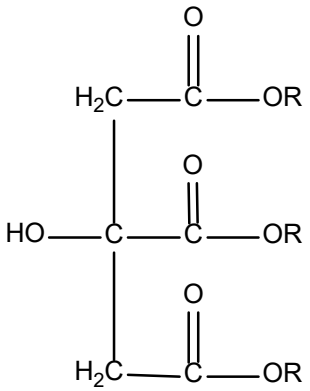
ADDITIVES/ADJUVANTS
None

4. IDENTITY OF ANALOGUE

CAS NUMBER
Unknown

CHEMICAL NAME
2-Hydroxypropane-1,2,3-tricarboxylic acid, tri (hexyl, octyl, decyl) ester

STRUCTURAL FORMULA



R = C6, C8, C10 alkyl group

OTHER NAME(S)
Tri (hexyl, octyl, decyl) citrate

MOLECULAR FORMULA
$C_{24}H_{44}O_7$ – $C_{36}H_{68}O_7$

JUSTIFICATION
The notified chemical and the analogue have the same basic structure – both are triesters of citric acid. The difference between the notified chemical and the analogue lies in the chain length of the alcohol part of the esters (C_{14-15} versus C_{6-10}) with the analogue being shorter in chain length. Its molecular weight is therefore smaller. This makes the analogue more readily absorbed compared to the notified chemical. The read-across data from the analogue anticipates values that are therefore more conservative compared to the notified chemical.

5. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: White flakes

Property	Value	Data Source/Justification
Melting Point/Freezing Point	46 °C at 101.3 kPa	(M)SDS
Boiling Point	>250 °C at 101.3 kPa	(M)SDS
Density	890 kg/m^3 at 70 °C	(M)SDS
Viscosity	0.019 N-s/m^2	(M)SDS
Vapour Pressure	8.25 x 10^{-24} - 1.85 x 10^{-22} kPa at 25 °C	Estimated (EPI Suite)
Water Solubility	<1.0 g/L at 25 °C; 3.85 × 10^{-19} - 1.34 × 10^{-17} g/L at 25 °C	Technical report (SASOL, 2012); Estimated by the notifier using EPI Suite 4.1 (US EPA, 2011)
Hydrolysis as a Function of pH	Not determined	The notified chemical contains hydrolysable functionality. However, based on its low water solubility, hydrolysis is expected to be very slow in the environmental pH range (4-9) at ambient temperature.
Partition Coefficient	log P_{ow} > 3 at 20 °C	(M)SDS

(n-octanol/water)	log P_{ow} = 18.0-19.5 at 25 °C	Estimated by the notifier using EPI Suite 4.1 (US EPA, 2011)
Adsorption/Desorption	log K_{oc} = 10.3-11.2 at 25 °C	Estimated by the notifier using EPI Suite 4.1 (US EPA, 2011)
Dissociation Constant	Not determined	The notified chemical does not contain functional groups that are expected to dissociate under typical environmental conditions.
Particle Size	Not determined	Material is in flake form
Flash Point	182 °C at 101.3 kPa	(M)SDS
Autoignition Temperature	Not determined	Expected to be high on the basis of the flash point.
Explosive Properties	Not determined	The notified chemical contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	The notified chemical contains no functional groups that would imply oxidative properties.

DISCUSSION OF PROPERTIES

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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6. INTRODUCTION AND USE INFORMATION

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

The notified chemical will be imported into Australia as a component of cosmetic products.

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

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

PORT OF ENTRY

Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS

L'Oreal Australia Pty Ltd

TRANSPORTATION AND PACKAGING

The cosmetic products containing the notified chemical (at ≤10% concentration) will be imported in sea containers. The end products in ≤500 mL plastic/HDPE bottles or tubes will be packaged in shipper cartons which will be arranged in pallets inside the sea containers. The notified chemical may also be imported as a neat chemical (at 100% concentration) for formulation into cosmetic products in Australia.

USE

The notified chemical will be used as a component (at ≤10% concentration) of cosmetic products such as rinse-off and leave-on formulations, lip and eye make-up.

OPERATION DESCRIPTION

The notified chemical is not manufactured in Australia. It will be contained (at ≤10% concentration) in finished imported cosmetic products. It may also be imported as a neat chemical (at 100% concentration) for formulation into cosmetic products (at ≤10% concentration).

The procedure for reformulation of the imported notified chemical (at 100% concentration) will likely vary depending on the nature of the cosmetic product formulated and may involve both automated and manual transfer steps. However, in general, it is expected that the formulation process will involve blending operations that will be highly automated and occur in a fully enclosed environment, followed by automated filling of the formulated products into containers of various sizes.

The finished products containing the notified chemical (at ≤10% concentration) may be used by consumers and professionals such as hairdressers and workers in beauty salons. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

7. HUMAN HEALTH IMPLICATIONS

7.1. Exposure Assessment

7.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	8	12
Compounder	8	12
Chemist/quality control	3	12
Packers	8	12
Hairdressers	Unspecified	Unspecified
Salon workers	Unspecified	Unspecified

EXPOSURE DETAILS

Transport and storage workers may come in contact with the notified chemical as a neat chemical (at ≤100% concentration) or as a component of cosmetic products (at ≤10% concentration), only in the event of accidental rupture of containers.

During formulation, dermal, ocular and inhalation exposure to the notified chemical (at ≤100% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as coveralls, safety glasses and impervious gloves.

Exposure to the notified chemical in end-use products (at ≤10% concentration) may occur in professions where the services provided involve the application of cosmetic products to the clients (e.g. hair dressers, workers in beauty salons). 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 similar or lesser extent than that experienced by consumers using products containing the notified chemical.

7.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤10% concentration) through the use of lip, eye and other leave-on and rinse-off cosmetic products. The principal routes of exposure will be dermal and oral with ocular and inhalation exposure being of a secondary nature.

Data on typical use patterns of cosmetic product categories in which the notified chemical may be used are shown in the tables below (SCCS, 2012; Cadby et al., 2002). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. An adult bodyweight of 60 kg was used for calculation purposes.

Dermal absorption is estimated to be 10% as the notified chemical has both a molecular weight > 500 Da and a partition coefficient (log $K_{o/w}$) > 4 (EC, 2004; SCCS, 2010).

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the tables below that contain the notified chemical, including those used near the mouth that may be ingested (e.g. lipstick/gloss).

Cosmetic products (dermal exposure):

Product Type	Amount (mg/day)	C (%)	RF	Daily Systemic Exposure (mg/kg bw/day)
Body lotion	7820	10	1	13.03
Face cream	1540	10	1	2.57
Hand cream	2160	10	1	3.60
Deodorant (non-spray)	1500	10	1	2.50
Liquid Foundation	510	10	1	0.85
Lipstick, lip salve	57	10	1	0.1
Mascara	25	10	1	0.04
Eyeliner	5	10	1	0.01
Eye shadow	20	10	1	0.03
Hair styling products	4000	10	0.1	0.67
Shower gel	18670	10	0.01	0.31
Hand wash soap	20000	10	0.01	0.33
Shampoo	10460	10	0.01	0.17
Hair conditioner	3920	10	0.01	0.07
Total				**24.29**

C - concentration; RF - retention factor.
Daily systemic exposure = Amount × C × RF/body weight.

Cosmetic products (oral exposure):

Product Type	Amount (mg/day)	C (%)	Daily Systemic Exposure (mg/kg bw/day)
Lipstick/gloss	57	10	0.1

Using a dermal absorption of 10% and oral availability of 100% results in a potential systemic dose of 2.52 mg/kg bw/day to the public from the use of the notified chemical in cosmetic products.

7.1. 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 A.

Endpoint	*Result and Assessment Conclusion*	*Source*
Rat, acute oral toxicity	LD50 >5000 mg/kg bw; low toxicity	notified chemical
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw; low toxicity	notified chemical
Humans, skin irritation	non-irritating	notified chemical
Rabbit, skin irritation	non-irritating	notified chemical
Eye irritation (in vitro)	non-irritating	notified chemical
Rabbit, eye irritation	slightly irritating	notified chemical
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation	notified chemical
Rat, repeated dose oral toxicity – 28 days.	NO(A)EL = 500 mg/kg bw/day	analogue chemical

Mutagenicity – bacterial reverse mutation	non mutagenic	notified chemical
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic	analogue chemical

Toxicokinetics, metabolism and distribution
The molecular weight of the notified chemical (781-823 Da), and its estimated high partition coefficient are likely to limit its absorption in the respiratory and GI tracts and across the skin.

Acute toxicity
The notified chemical was found to be of low acute dermal (LD_{50} >2000 mg/kg) and oral (LD_{50} >5000 mg/kg) toxicity in the rat. There were no signs of systemic effects observed in both studies. The noted gain in body weight in both studies was considered normal for the species and strain used.

There were no data available on the acute inhalation toxicity of the notified chemical.

Irritation
The notified chemical was non-irritating to the skin of rabbits and to human skin in a single-dose.

The notified chemical was slightly irritating to the rabbit eye, with conjunctival effects that had resolved by 72h. It was negative in the *in vitro* chorioallantoic membrane test. However the latter test protocol is not validated.

The notified chemical was found to be non-comedogenic to slightly comedogenic in 15 human volunteers.

Sensitisation
The notified chemical did not show evidence of skin sensitisation in the guinea pig (Magnusson and Kligman).

Repeated Dose Toxicity
A 28-day repeated dose study by oral gavage was conducted in rats to OECD guidelines, using the analogue chemical. There were no overt signs of toxicity or unscheduled deaths. There were no significant differences in weight gain and food consumption between treated and control animals. Organ weight changes in the kidney and the thymus in females and the adrenal and the epididymis in males did not have a dose-response relationship except in the epididymis weights. The latter was attributed to a non-significant slight decrease in body weight gains in all treated animals. At the highest treatment group of 1000 mg/kg bw/day, one male animal had gastric glandular erosion and one female animal had intracytoplasmic inclusions as well as submucosal inflammation in the gastric glandular mucosa. Based on the histopathology findings at 1000 mg/kg bw/day from the analogue chemical a NO(A)EL of 500 mg/kg bw/day was used in the risk assessment for the notified chemical.

Mutagenicity
The notified chemical was not mutagenic in a bacterial reverse mutation study, nor clastogenic in an *in vitro* mammalian chromosome aberration test (conducted to OECD guidelines).

Health hazard classification

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

7.2. Human Health Risk Characterisation

7.3.1. Occupational Health and Safety

Blending
Dermal and ocular exposure of workers to the notified chemical (at 100% concentration) will occur during reformulation processes. Given that the exposure of workers is expected to be minimised through the use of automated processes, ventilated environments and wearing of PPE, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use

Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical (at ≤10% concentration) to clients (e.g. beauty salon workers) may be exposed to the notified chemical. The inhalation risk to beauty salon workers is expected to be low, given the notified chemical's properties (molecular weight, partition coefficient and vapour pressure). Based on use of PPE (gloves), the dermal risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 7.3.2.).

7.3.2. Public Health

At the proposed usage concentration of ≤10% notified chemical (in lip, eye and other leave-on and rinse-off cosmetic products), acute toxicity effects are not expected.

The repeated dose toxicity potential was estimated by calculation of the MoE of the notified chemical using the worst case exposure scenario from the use of multiple products of 2.52 mg/kg bw/day (see Section 7.1.2.). Using a NO(A)EL of 500 mg/kg bw/day, which was derived from a 28-day repeated dose toxicity study on the analogue chemical, the margin of exposure (MoE) was estimated to be 198. In general, a MoE value ≥100 is considered acceptable to account for intra- and inter-species differences. Overall, based on the available information, the risk to the public from use of the notified chemical at ≤10% in lip, eye and other leave-on and rinse-off cosmetic products is not considered to be unreasonable.

8. ENVIRONMENTAL IMPLICATIONS

8.1. Environmental Exposure & Fate Assessment

8.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of finished cosmetic products and may also be imported as a neat chemical for formulation into cosmetic products. Accidental spills are expected to be collected with inert material and disposed of to landfill. Some of the notified chemical may be released to sewer during equipment cleaning where reformulation activities take place.

RELEASE OF CHEMICAL FROM USE
The notified chemical will be used as a component of cosmetic products, specifically rinse-off and leave-on formulations such as lip and eye products. It is expected that the majority of the imported quantity of notified chemical will eventually be washed off the skin and released to sewer.

RELEASE OF CHEMICAL FROM DISPOSAL
Residual notified chemical remaining in empty import containers (1% of the total import volume) and end-use containers is expected to be disposed of to landfill along with the containers, or to be washed to sewer when containers are rinsed before recycling.

8.1.2. Environmental Fate

The majority of the notified chemical is expected to be released to sewer during use in cosmetic products. During waste water treatment processes in sewage treatment plants (STPs), most of the notified chemical is expected to be removed from waste waters by sorption to sludge due to its hydrophobic structure. The notified chemical that partitions and/or adsorbs to sludge will be removed with the sludge for disposal to landfill or used in soil remediation. The quantity of the notified chemical that is released to surface waters is expected to be very low due to its very low water solubility. However, if it reaches receiving waters, it is expected to partition and/or adsorb to suspended solids and organic matter, and disperse and degrade.

The analogue chemical is considered applicable as read across to the notified chemical with regards to biodegradability as they have the same basic structure, triesters of citric acid. The analogue chemical is considered inherently biodegradable (67% over 28 days) although it did not pass the 10-day window for it to be classified as readily biodegradable. Hence, the notified chemical is expected to biodegrade in a similar manner as its analogue. Since the notified chemical has low water solubility and rapid degradability, it is not expected to be significantly bioavailable in receiving waters. Therefore, the bioavailable fraction of the notified chemical in

the receiving waters is expected to be low. Although the notified chemical is likely to bioaccumulate due to its hydrophobic structure, it may be negligible due to its low bioavailability and rapid degradability.

8.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported uses in cosmetic products, it is assumed that 100% of the notified chemical will be released to sewer on a nationwide basis over 365 days per year. It is also assumed that under a worst-case scenario that there is no removal of the notified chemical during STP processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment			
Total Annual Import/Manufactured Volume	3,000		kg/year
Proportion expected to be released to sewer	100%		
Annual quantity of chemical released to sewer		3,000	kg/year
Days per year where release occurs	365		days/year
Daily chemical release:	8.22		kg/day
Water use	200		L/person/day
Population of Australia (Millions)	22.613		million
Removal within STP	0%		
Daily effluent production:	4,523		ML
Dilution Factor - River	1		
Dilution Factor - Ocean	10		
PEC - River:	1.82		µg/L
PEC - Ocean:	0.18		µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 1.82 µg/L may potentially result in a soil concentration of approximately 12.12 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 60.58 µg/kg and 121.2 µg/kg, respectively.

8.2. Environmental Effects Assessment

The result from ecotoxicological investigations conducted on the analogue chemical is summarised in the table below. The analogue substance (tri (hexyl, octyl, decyl) citrate) was used as read across to the notified chemical due to their similar generic molecular structure. The reported analogue endpoint for daphnia toxicity exceeds the water solubility limit of the notified chemical, suggesting that aquatic toxicology would not be expected at water saturated levels. The notified chemical is not anticipated to be bioavailable as it is expected to have a high log K_{ow} value. Therefore, no effects on aquatic biota are predicted for the notified chemical at its water saturation concentration (ECOSAR (v1.11), US EPA, 2012).

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity	48 h EC50 > limit of water solubility	Not harmful to aquatic invertebrates up to the limit of water solubility

The toxicity endpoint for daphnia was not related to a specific concentration of the test substance but only to the water solubility limit in the test medium. Classification should only be based on toxic responses observed in the soluble range and, therefore, the notified chemical cannot be formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009).

8.2.1. Predicted No-Effect Concentration

No toxicity effects are to be expected at the limit of solubility for the notified chemical, and therefore the predicted no-effect concentration (PNEC) cannot be calculated.

8.3. Environmental Risk Assessment

A risk quotient (PEC/PNEC) for the notified chemical was not calculated as a PNEC was not derived. Based on the analogue data, the notified chemical is expected to be rapidly biodegradable in the environment. Additionally, it has low potential to be bioavailable due to its low water solubility. The notified chemical is not expected to be harmful to aquatic organisms up to the limit of its solubility. Therefore, the notified chemical is not expected to pose an unreasonable risk to the environment based on the assessed use pattern.

APPENDIX A: TOXICOLOGICAL INVESTIGATIONS

A.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.

Species/Strain	Rat/Wistar
Vehicle	Sesame seed oil
Remarks - Method	The test substance was administered by gavage.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M / 5F	5000	nil

LD50	>5000 mg/kg bw
Signs of Toxicity	None
Effects in Organs	None
Remarks - Results	The body weight gain was considered normal for the species and strain used in the study.

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

TEST FACILITY: Biolab SGS (1992a)

A.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test.

Species/Strain	Rat/Wistar
Vehicle	None
Type of dressing	Occlusive
Remarks - Method	No GLP statement was included in the report. After the 24 h test period, excess material was washed from the skin with a pad soaked in distilled water.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M / 5F	2000	nil

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	None
Signs of Toxicity - Systemic	None
Effects in Organs	None
Remarks - Results	The body weight gain was considered normal for the species and strain used in the study.

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

TEST FACILITY: Biolab SGS (1993a)

A.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	6M
Vehicle	Sesame seed oil
Observation Period	4 hr
Type of Dressing	Occlusive
Remarks - Method	A paste of the test substance in the vehicle (500 mg in 0.5 mL) was applied to a 20 cm^2 area on the right flank. After the 4 h treatment period, excess material was washed from the skin with a pad soaked in distilled water. Reactions were evaluated following removal of the patches and at 24, 48 and 72 hr after exposure.
Remarks - Results	No erythema and oedema were observed in all treated animals during the study.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Biolab SGS (1992d)

A.4. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	Human Patch Test – single administration
Species/Strain	Human volunteers
Number of Volunteers	15M and 23F
Vehicle	None
Observation Period	48 hr
Type of Dressing	Occlusive
Remarks - Method	The 38 volunteers were between 18-65 years old. Each volunteer served as his/her own control, having a treated and non-treated area. The test material was applied at a dose of 0.5 mL in a 1 cm^2 area of skin on the back. The reactions were evaluated 15 min and 24 hr after removal of the patches. The results were interpreted in accordance with the Draize Method.
Remarks - Results	No erythema/eschar formation and oedema formation were observed in any of the 38 volunteers. The total irritation index and the medium irritation index at 15min and 24 hr were 0.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Biolab SGS (1993b)

A.5. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	6M
Observation Period	72 hr
Remarks - Method	Conjunctival discharge was not one of the parameters reported in the study.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*

Conjunctiva: redness	0.33	1	<72 hr	0
Conjunctiva: chemosis	0.0	0	-	0
Corneal opacity	0.0	0	-	0
Iridial inflammation	0.0	0	-	0

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

Remarks - Results: Individual scores were not reported, only the mean score for each parameter at each observation time.

CONCLUSION: The notified chemical is slightly irritating to the eye.

TEST FACILITY: Biolab SGS (1992b)

A.6. Irritation – eye

TEST SUBSTANCE: Notified chemical

METHOD: The Chorioallantoic Membrane (CAM) Test for Predicting Ocular Irritancy. Modification of that described by Kemper and Luepke as Hen's Egg Test (1986).

Species/Strain: Ross chicken eggs

Remarks - Method: Day 10 eggs (in triplicate) were fertilised and incubated for the test substance, negative (sterile water) and positive (glacial acetic acid) controls. Readings taken during a 5 min period. The test substance was applied as approximately 100 mg aliquots directly to the CAM surface and left in contact with the membrane for 20 sec followed by irrigation with warm sterile water. Effects of hyperemia, haemorrhage (including minimal haemorrhage) and coagulation were investigated during the period of 5 mins for scoring.

RESULTS

Test Solution	*Average Irritation score*
Sterile water	0.0
Notified polymer	0.0
Glacial acetic acid)	10.0

Remarks - Results: No reactions were detected in the eggs treated with the test substance.

CONCLUSION: The notified chemical is predicted to be non-irritating to the eye.

TEST FACILITY: Pharmaco-LSR (1994)

A.7. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 406 Skin Sensitisation – Maximisation Test.

Species/Strain: Guinea pig/Hartley Albino

MAIN STUDY

Number of Animals: Test Group: 20F Control Group: 10F

INDUCTION PHASE: Induction Concentration:
intradermal: 50%
topical 100%

Signs of Irritation: Not recorded

CHALLENGE PHASE

1st challenge: topical: 100%

Remarks - Method: The study was conducted in June 1992 prior to the publication of OECD TG 406. However there were no significant deviations from the protocol. No preliminary study or rechallenge were performed.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h & 72 h*	*24 h*	*48 h*
Test Group	100%	0	0	N/A	N/A
Control Group	100%	0	0	N/A	N/A

Remarks - Results There were no signs of erythema and/or oedema observed in treated or control animals during after challenge.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY Biolab SGS (1992f)

A.8. Repeat dose toxicity

TEST SUBSTANCE Analogue chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain Rat/HSDBrl:WH Wistar
Route of Administration Oral – gavage
Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: none
Vehicle 1% Carboxymethylcellulose aqueous solution

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M, 5F	0	0/10
low dose	5M, 5F	150	0/10
mid dose	5M, 5F	500	0/10
high dose	5M, 5F	1000	0/10

Mortality and Time to Death
There were no unscheduled deaths.

Body Weight Gain and Food Consumption
A slightly reduced (no statistical significance, no dose-response relationship) body weight gain was observed in both male and female animals in the treated groups. There were no significant reductions in food consumption in both male and female animals in the treated groups.

Clinical Observations
There were no signs of clinical toxicity observed in any of the treated animals.

Behavioural/Functional Observations
There were no significant changes in behavioural and functional parameters. There was a slight increase in the frequency of supported rears in most treatment groups and a significant increase in unassisted rears in most treatment groups observed at week 4.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No dose-dependent and statistically significant changes were observed in clinical biochemistry values except for GOT where a statistically significant increase over the controls was noted at 500 mg/kg bw/day in males only, but not at the low and high treatment doses. This increase was not considered biologically relevant as there was no dose response, and the levels were within the expected values. No dose-dependent and

statistically significant changes were seen in haematology and urinalysis results.

Effects in Organs

There were some statistically significant differences in organ weight assessment without clear dose dependency. They are as follows: (1) in females at 150 mg/kg bw/day, relative kidney weights increased, and absolute and relative thymus weights decreased; no such effects were seen at the mid and high treatment doses; and (2) in males the relative epididymis weights were significantly reduced at all treatment groups and the absolute epididymis weights were only significantly reduced at 150 mg/kg bw/day.

Also in males, absolute adrenal weights were significantly decreased at 1000 mg/kg bw/day (the reduction observed at 500 and 150 mg/kg bw/day was without statistical significance). The significance of this weight reduction in the adrenals is not clear in the absence of other correlating changes and in light of the relative adrenal weights at all treatment groups being within limits.

The observed increase in the weights of the epididymides was attributed by the study authors to the slight decrease in body weight gains in all treatment groups.

Histopathology

At the highest treatment group, one male animal had gastric glandular erosion and one female animal had intracytoplasmic inclusions in the gastric glandular mucosa as well as inflammation in the gastric glandular submucosa. The study authors were unsure whether these might be precursors of adverse effects in that organ, or whether, as occasionally happens in control animals, they were a random effect unrelated to treatment.

All other morphological changes were those observed in laboratory maintained rats of the age and strain employed and there were no differences in incidence between the control and treatment groups considered to be of toxicological significance.

Remarks – Results

The study authors established a NO(A)EL of 1000 mg/kg bw/day based on the absence of effects with clear dose-related dependency and biological significance. However for this short term repeated dose study where histopathological changes were seen at the highest dose, adverse effects from a longer exposure period are possible.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) is established as 500 mg/kg bw/day in this study, based on histopathological effects seen in the glandular stomachs in two animals (one per sex) at the highest dose: the male animal displayed gastric glandular erosion and the female animal displayed both epithelial inclusions and submucosal inflammation in the glandular stomach.

TEST FACILITY BSL Bioservice (1999a)

A.9. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test.

	Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100
Metabolic Activation System	S9 from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 1-10,000 µg/plate b) Without metabolic activation: 1-10,000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No GLP statement was included in the report. Doses were chosen on the basis of a preliminary toxicity test. Only one main test was performed.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	*	> 10,000	**	none

Present				
Test 1	*	> 10,000	**	none

* Details of the preliminary test were not reported.
** It was not reported whether precipitation occurred.

Remarks - Results: The number of revertant colonies in the vehicle-treated control was within the normal range, and the positive controls were all mutagenic in their appropriate tester strain, confirming the validity of the test.

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

TEST FACILITY: Biolab SGS (1992e)

A.10. Genotoxicity – in vitro

TEST SUBSTANCE: Analogue chemical

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain: Chinese hamster
Cell Type/Cell Line: V79 cells
Metabolic Activation System: S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Vehicle: Dimethyl sulfoxide
Remarks - Method: No significant protocol deviations.
A preliminary toxicity test was performed to define the toxicity of the test material.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	100*, 2500*, 5000*	4 hr	20 hr
Test 2a	5*, 10*, 25*	20 hr	20 hr
Test 2b	25*	28 hr	28 hr
Present			
Test 1	250*, 2500*, 5000*	4 hr	20 hr
Test 2	5000*	4 hr	28 hr

*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	≥1250	>5000	>250	Negative
Test 2a		>25	>250	Negative
Test 2b		>25	>250	Negative
Present				
Test 1	>5000	>5000	>250	Negative
Test 2		>5000	>250	Negative

Remarks - Results: The doses for test 1 were chosen on the basis of a preliminary toxicity study (not reported). The doses for test 2 were adjusted because of unexpected toxicity effects seen in test 1 in the absence of metabolic activation
With and without metabolic activation, the analogue substance did not increase the frequency of cells with aberrations in either test 1 or test 2.

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

TEST FACILITY	BSL Bioservice (1999b)

A.11. Comedogenicity

TEST SUBSTANCE	Notified chemical
METHOD	In-house
Species/Strain	Human volunteers (7M; 8F)
Remarks - Method	The test was performed by single dose occlusive application of 0.5 ml of test substance (vehicle was not described) and negative control (substance was not described) on 1 cm^2 area of skin of the interscapular region for 48 hours (distance between areas for control and test substances was not described). The excess material was removed and the application was repeated for 48 hours. The procedure was repeated three times per week for one month. During inclusions a mould was taken using silicon resin of the area to be treated for visual analysis at 50x, 200x and 500x magnifications using an instrument consisting of an optical fibre probe connected to a screen. Skin reactions were evaluated 15 minutes after patch removal for the formation of the following: erythema and eschar, oedema and comedores. For comedogenicity, numerical scoring was used: < 0.5 (non comedogenic); 0.5-1 (slightly comedogenic); 1-2 (moderately comedogenic); 2-3 (strongly comedogenic); and 3-5 (comedogenic and irritant).
RESULTS	The following values were scored for the test substance: 0.27 (week 1); 0.53 (week 2); 0.6 (week 3); and 0.6 (week 4).
CONCLUSION	The test substance was non-comedogenic to slightly comedogenic to humans.
TEST FACILITY	Biolab SRL (1994)

APPENDIX B: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

B.1. Environmental Fate

B.1.1. Ready biodegradability

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	TOC-analyser for dissolved organic carbon (DOC) and CO_2 evolution analysis
Remarks - Method	In case of poorly soluble compounds the test substance was added directly into the test vessels. The test was conducted in accordance with the test guideline above without significant deviation from the protocol. Good laboratory practice (GLP) standards were followed.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
7	19	7	75
13	46	13	85
20	59	20	85
28	67	28	87

Remarks - Results	The biodegradation of the test substance reached 51% at the end of the 10-d window and did not pass the ready biodegradability level of 60% in the CO_2 evolution test. However, significant degradation of the test substance was observed after 21 days. It can therefore be considered as inherently biodegradable. Due to the limited water solubility of the test substance, biodegradation based on DOC measurements could not be assessed. The toxicity control was not performed in the test, therefore it is not clear whether the test substance is toxic to the microorganisms in the test media. All other validity criteria were satisfied.
CONCLUSION	The test substance and, by inference, the notified chemical are considered to be inherently biodegradable.
TEST FACILITY	BMG (1999)

B.2. Ecotoxicological Investigations

B.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	N/A
Remarks - Method	No concentrations in excess of the water solubility limit of the test

substance were tested. A supersaturated stock suspension of the test substance with a nominal concentration of 100 mg/L was prepared by mixing the test substance with water. The mixture was homogenised by ultrasonic treatment for 10 minutes and intense stirring, followed with 3-day stirring at room temperature. The prepared suspension was filtered just before use.

The only concentration tested was the undiluted filtrate of the supersaturated stock suspension. The limit test was conducted in accordance with the test guideline above. The study was performed in compliance with good laboratory practice (GLP).

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	N/A	20	0	0
100 mg/L	Limit of water solubility	20	0	0

EC50	> the limit of water solubility at 48 hours
NOEC	> the limit of water solubility
Remarks - Results	The 48-hour EC50 could not be quantified due the absence of toxicity of the test substance up to the tested concentration. This value is expected to be higher than the solubility limit of the test substance in the test medium. Due to the low water solubility, no analytical concentration was verified in the test. Therefore, the biological results were not related to a specific concentration of the test substance but only to the water solubility limit in the test medium.

CONCLUSION The test substance and, by inference, the notified chemical, are not harmful to aquatic invertebrates up to the limit of water solubility.

TEST FACILITY IBACON (1999)

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