File No: LTD/1805

February 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, 1,2,3-tris(2-octyldodecyl) ester (INCI name: Trioctyldodecyl citrate)

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.

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
LTD/1805	Estee Lauder Pty Ltd	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, 1,2,3-tris(2-octyldodecyl) ester (INCI name: Trioctyldodecyl citrate)	ND	≤ 995 kg per annum	Ingredient in cosmetics

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on limited available information, 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 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
Based on the assumed low hazard and 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 engineering controls to minimise occupational exposure to the notified chemical.

- 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 in the product:
  - Disposable gloves
  - Safety glasses

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

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

Disposal

- Where reuse or recycling are not appropriate, dispose 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 importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical is intended to exceed 30% in make-up products and/or 12% in other cosmetic products;

or

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

The notified chemical is currently on the AICS with the following conditions of use:

- For cosmetic use only
- For dermal use only
- The concentration is not to exceed 12%
- It is not to be included in topical products intended for use in the eye.

The notified chemical is proposed to be used at ≤ 30% concentration in make-up products (e.g. liquid foundation, eye shadow, mascara, eyeliner and lipsticks) and at ≤ 10% concentration in other cosmetics. Noting that the chemical may be used in cosmetic products at ≤ 12% concentration under the current AICS use conditions, this assessment is for use of the notified chemical in make-up products only at ≤ 30% concentration.

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Estee Lauder Pty Ltd (ABN: 63 008 444 719)
165-175 Mitchell Road
Erskineville NSW 2043

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: all physico-chemical properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Citmol 320
Siltech CE-2000

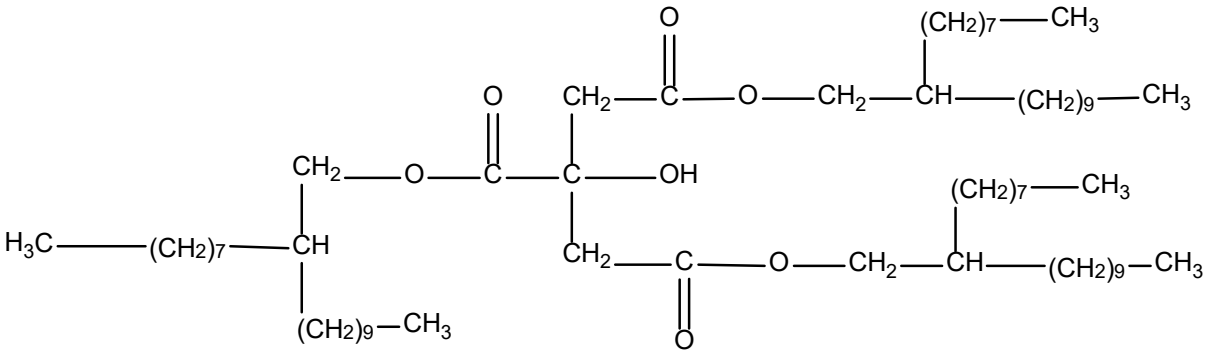
CAS NUMBER
126121-35-5

CHEMICAL NAME
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, 1,2,3-tris(2-octyldodecyl) ester

OTHER NAME(S)
Trioctyldodecyl citrate (INCI name)

MOLECULAR FORMULA
$C_{66}H_{128}O_7$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
1033.72 Da

ANALYTICAL DATA
Reference IR and GPC spectra were provided.

3. IDENTITY OF ANALOGUES

Limited toxicological data were provided for the notified chemical. Therefore toxicological information from two structurally similar analogue chemicals was used for human health effect assessment.

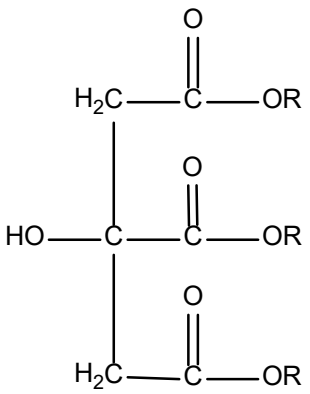
JUSTIFICATION
The notified chemical and the analogues have the same basic structure, triesters of citric acid. The difference between the notified chemical and the analogues lies in the chain length of the alcohol part of the esters (C_{20} versus $C_{6\text{-}10}$ and $C_{14\text{-}15}$). The molecular weights of the analogues are smaller in comparison to the notified chemical, implying that the analogues may be more readily absorbed compared to the notified chemical. The read-across data from the analogues anticipates values that are therefore more conservative compared to the notified chemical.

ANALOGUE CHEMICAL 1

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

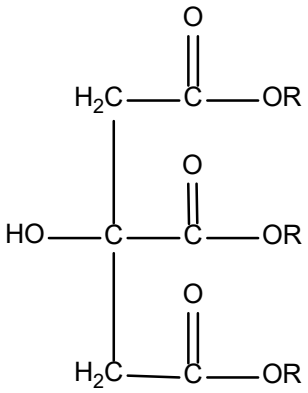
MOLECULAR WEIGHT
445-613 Da

ANALOGUE CHEMICAL 2

CAS NUMBER
222721-94-0

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

STRUCTURAL FORMULA



R = C14- C15 alkyl group

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

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

MOLECULAR WEIGHT
781-823 Da

4. COMPOSITION

DEGREE OF PURITY
90-95 %

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

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

Chemical Name	1-Dodecanol, 2-octyl-		
CAS No.	5333-42-6	*Weight %*	5-10

ADDITIVES/ADJUVANTS
None

5. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< 20 °C	(M)SDS
Boiling Point	> 200 °C at 101.3 kPa	(M)SDS
Density	890 kg/m^3 at 25 °C	(M)SDS
Vapour Pressure	1×10^{-29} kPa at 20 °C	Calculated (EPI Suite)
Water Solubility	Not determined	Expected to be low based on predominantly hydrophobic structure of the notified chemical.
Hydrolysis as a Function of pH	Not determined	The notified chemical contains hydrolysable functionality. However, based on its expected low water solubility, hydrolysis is expected to be very slow in the environmental pH range (4-9).
Partition Coefficient (n-octanol/water)	Not determined	Expected to partition to n-octanol based on its expected low water solubility.
Adsorption/Desorption	Not determined	Expected to adsorb to sediment/sludge based on its expected low water solubility and high molecular weight.
Dissociation Constant	Not determined	The notified chemical does not contain ionisable functionalities.
Flash Point	> 200 °C (Pensky Martens closed cup)	(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 finished cosmetic products.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.5	0.6	0.7	0.8	0.995

PORT OF ENTRY
Sydney by wharf

IDENTITY OF RECIPIENTS
Estee Lauder Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as an ingredient in finished cosmetic products. These products in 3 – 10 g containers will be packed in cardboard shipper and transported in a container from the wharf to the warehouse. Cartons will be transported to principal retail stores and central distribution centres by road.

USE
The notified chemical will be used as an ingredient in make-up products (e.g. liquid foundation, eye shadow, mascara, eyeliner and lipsticks) at ≤ 30% concentration.

OPERATION DESCRIPTION
The notified chemical will not be manufactured or reformulated in Australia. It will be imported in finished cosmetic products at ≤ 30% concentration.

The finished products containing the notified chemical (at ≤ 30% concentration) will be used by the public and beauty salon professionals. Depending on the nature of the products, these are expected to be applied in a number of ways, such as by hand or by using an applicator.

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	4	12
Packers	4	12
End Users(e.g. beauty salon workers)	8	365

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical as a component of cosmetic products (at ≤ 30% concentration), only in the event of accidental rupture of containers.

Exposure to the notified chemical in end-use products (at ≤ 30% concentration) may occur in professions where the services provided involve the application of cosmetic products to the clients (e.g. workers in beauty salons). Such professionals may use some personal protective equipment (PPE), such as gloves 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 up to 30% concentration in make-up cosmetic products. The main route of exposure will be dermal.

Based on SCCS (2012), data on typical use patterns of cosmetic product categories in which the notified chemical may be used are estimated in the table below. For the purpose of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. An average adult bodyweight of 60 kg was used for calculation purposes. The dermal absorption of the notified chemical is estimated to be 10%, as the chemical has both a molecular weight > 500 Da and an expected partition coefficient (log K_{ow}) > 4 (EC, 2004; SCCS, 2012).

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

Product type	***Amount*** *(mg/day)*	***C*** *(%)*	***RF***	***Absorption*** ***(%)***	***Daily systemic exposure*** *(mg/kg bw/day)*
Liquid Foundation	510	30	1	10	0.255
Lipstick, lip salve*	57	30	1	100	0.285
Mascara	25	30	1	10	0.013
Eyeliner	5	30	1	10	0.003
Eye shadow	20	30	1	10	0.010
Total					**0.565**

* Assuming 100% oral availability for the products used on lip
C – Proposed use concentration; RF - Retention factor.
Daily systemic exposure = Amount × C × RF × Absorption / body weight.

Using a dermal absorption of 10% and oral availability of 100% will result in a total potential systemic dose of 0.565 mg/kg bw/day to the public from the combined use of make-up products containing the notified chemical.

7.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical or its analogues 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 > 5000mg/kg bw; low toxicity	Notified chemical
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity	Analogue 2
Rabbit, skin irritation (*in vivo*)	Slightly irritating	Notified chemical
Rabbit, eye irritation (*in vivo*)	Non-irritating	Notified chemical
Mouse, skin sensitisation – Local lymph node assay	Evidence of sensitisation	Notified chemical
Human, skin sensitisation – RIPT (tested at 14.7 % concentration)	No evidence of sensitisation	Notified chemical
Human, skin sensitisation – RIPT (tested at 29.44% concentration)	No evidence of sensitisation	Notified chemical
Rat, repeat dose oral toxicity – 28 days	NOAEL = 500 mg/kg bw/day	Analogue 1
Mutagenicity – bacterial reverse mutation	Non mutagenic	Analogue 2
Genotoxicity – *in vitro* mammalian chromosome aberration test	Non genotoxic	Analogue 1

Toxicokinetics, metabolism and distribution

The molecular weight of the notified chemical (1033.72 Da) and its expected high partition coefficient are likely to limit its absorption in the respiratory and GI tracts and across the skin (EC, 2004; SCCS, 2012).

Acute toxicity

The notified chemical was found to be of low acute oral toxicity in rats (LD_{50} > 5000 mg/kg bw). There were no overt signs of toxicity or unscheduled deaths.

In an acute dermal toxicity study on rats, the Analogue 2 was also found to be of low toxicity via the dermal route with LD50 > 2000 mg/kg bw. There were no signs of systemic effects observed.

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

Irritation and skin sensitisation

The notified chemical was slightly irritating to the skin and non–irritating to the eyes of rabbits at 25% concentration. Analogue 2 was found to be non-comedogenic to slightly comedogenic in 15 human volunteers.

Two human repeated insult patch tests (HRIPTs) were conducted on 112 and 113 subjects with cosmetic products containing the notified chemical at concentrations 14.9% and 29.4%, respectively. The studies reported no evidence of sensitisation for the notified chemical on human skin. A Cosmetic Ingredient Review (CIR, 2012) reported that the notified chemical was tested at 100% concentration on 105 subjects. The notified chemical was applied four times a week for three weeks followed by four challenge applications on a previously untreated area. The study reported that the notified chemical was not an irritant or a sensitiser. However, based on a statement provided by the notifier and the above CIR report, a local lymph node assay (LLNA) with the notified chemical at concentrations 10, 50, 100% on mice found that the chemical is a sensitiser. The notified chemical was applied daily for 3 days. Untreated and positive (α-hexylcinnamic aldehyde) controls were used. The stimulation index (SI) for the concentrations tested ranged from 1.1 to 3.1 and the EC3 value was calculated to be 95.8%. It was concluded that the notified chemical should be considered to have potential to cause sensitisation by skin contact. The full report of the LLNA study was not provided.

Repeated dose toxicity
A 28-day repeated dose study by oral gavage was conducted in rats to OECD guidelines, using Analogue 1. 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 in males did not have a dose-response relationship. The epididymis weight change in males 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 NOAEL of 500 mg/kg bw/day from this study was used in the quantitative risk assessment for the notified chemical.

Mutagenicity/Genotoxicity
Analogue 2 was not mutagenic in a bacterial reverse mutation study, nor clastogenic in an *in vitro* mammalian chromosome aberration test (conducted to OECD guidelines).

7.3. Human Health Risk Characterisation

7.3.1. Occupational Health and Safety
The notified chemical will not be manufactured or reformulated in Australia. During transport and storage, exposure to the notified chemical at up to 30% concentration may occur in the event of accidental spills. Use of PPE will minimise the exposure during such events.

Beauty care professionals may come into contact with finished make-up products containing the notified chemical at up to 30% concentration. The risk to workers who regularly use these products is expected to be of a similar or lesser extent than that experienced by consumers using same products containing the notified chemical (for details of the public health risk assessment, see Section 7.3.2).

7.3.2. Public Health

Repeated exposure
Members of the public may experience repeated exposure to the notified chemical (at up to 30% concentration) through the use of the make-up products. The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from the use of multiple products, causing daily systemic uptake of the notified chemical at a level of 0.565 mg/kg bw/day (see Section 6.1.2.). Using a NOAEL of 500 mg/kg bw/day, which was derived from a 28-day repeated dose toxicity study on Analogue 1, the MoE was estimated to be 885. In general, a MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. It is noted that the notified chemical may be used in other cosmetic products at ≤ 12% concentration (as per the current AICS entry for the notified chemical) and the exposure to these products has not been accounted for in the exposure/risk assessment for the notified chemical. However, additional calculations undertaken by NICNAS showed that the derived MOE is sufficiently protective to cover additional exposure to the notified chemical from the potential use of other cosmetic products at ≤ 12% concentration.

Skin sensitisation
Based on available toxicology information, the notified chemical has the potential to cause skin sensitisation. Methods for the quantitative risk assessment for dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). The HRIPT information from the CIR (CIR, 2012) has been used for the purposes of quantitative risk assessment of the notified chemical. Additional information on the sensitisation potential of the notified chemical (e.g. the LLNA study) was also taken into account when determining the safety assessment factors to be applied. Thus, consideration of the study details and application of appropriate safety factors, allowed the derivation of an Acceptable Exposure Level (AEL) of 333.75 µg/cm^2 for the notified chemical. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), a use and time factor (3.16) and a database factor (1), giving an overall safety factor of approximately 100.

Using liquid foundation (containing 30% notified chemical) as an example make-up product that may contain the notified chemical, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 270.80 µg/cm^2 (SCCS, 2012). As the AEL>CEL, the risk to the public of induction of skin sensitisation that is associated with the use of the notified chemical in liquid foundation at up to 30% concentration is not considered to be unreasonable. As liquid foundation was considered to represent a worst case example of a make-up product, by inference, the risk of induction of sensitisation associated with the use of other make-up products at up to 30% concentration is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Irritation
The notified chemical was tested at a concentration of 25% for skin irritation effects and was found to be slightly irritating at that concentration (see Appendix A). Therefore, when using cosmetic products containing the notified chemical > 25%, the potential for slight skin irritation effects cannot be ruled out. However, the scores of the skin reaction in the above study were below the criteria for classification.

Based on the available information, when used at proposed concentrations under normal use conditions, the risk to the public from use of the notified chemical in 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 not be manufactured or reformulated in Australia. The notified chemical will be imported as finished cosmetic products. Therefore, release of the notified chemical from these activities is not expected. Accidental spills are expected to be collected with inert material and disposed of to landfill.

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 skin 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 (3% 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 a read across for the notified chemical with respect to biodegradability because 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 to 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. The notified chemical is not likely to bioaccumulate due to its high molecular weight.

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 conservatively 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	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.606 µg/L may potentially result in a soil concentration of approximately 4.04 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 20.2 µg/kg and 40.4 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 similarities in their generic molecular structures. 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) and given the high molecular weight of the notified chemical (MW > 1000).

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 inherently biodegradable in the environment. Additionally, it has low potential to be bioavailable due to its expected 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	None
Remarks - Method	Five male and five female rats each received a single oral dose of the test substance at a dose level of 5000 mg/kg bw. Animals were observed for pharmacologic activity and drug toxicity 1, 3, 6 and 24 hours after the treatment, and daily thereafter for a total of 14 days. Gross necropsy was conducted at the end of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5M	5000	0
II	5F	5000	0

LD50	>5 000 mg/kg bw
Signs of Toxicity	There were no deaths or remarkable bodyweight changes. Clinical sign such as moist rale was observed in two male rats after 6 hours during the study.
Effects in Organs	There were no remarkable necropsy findings.
Remarks - Results	All animals showed expected body weight gains during the study.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	CPT (1988)

A.2. Acute toxicity – dermal

TEST SUBSTANCE	Analogue chemical 2
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	0/10

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 (1993)

A.3. Irritation – skin

TEST SUBSTANCE	Notified chemical (25% in vehicle)
METHOD	Similar to OECD TG 404 Acute Dermal Irritation.
Species/Strain	Rabbit/New Zealand White
Number of Animals	Six
Vehicle	Corn oil
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	The percentage of the test material used was 25%. The test results were calculated for 24 hours and 72 hours only.

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Erythema/Eschar	1.5	1.5	1.5	1	0.5	2	2	> 72 hours	2
Oedema	0.75	0	0.5	0	0.5	0.5	1	< 72 hours	0

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

Remarks – Results	Skin irritation was studied on two locations on each animal and the mean of the results from both sites is presented above. Pustule was observed on both test sites on one animal.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	CPT (1988)

A.4. Irritation – eye

TEST SUBSTANCE	Notified chemical (25%)
METHOD	Similar to OECD TG 405 Acute Eye Irritation.
Species/Strain	Rabbit/New Zealand White
Number of Animals	Six
Observation Period	7 days
Remarks - Method	The percentage of the test material used was 25%.
Remarks - Results	No eye reactions with score above 0 were noted at 24, 48 and 72 hours in the test animals.
CONCLUSION	The notified chemical is non-irritating to the eye.
TEST FACILITY	CPT (1988)

A.5. Skin sensitisation – human volunteers (1)

TEST SUBSTANCE	Lipstick containing the notified chemical at 14.7%
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: The test substance was applied to the upper back and allowed to remain in direct skin contact for a period of 24 hours. Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications. Patch sites were graded for dermal irritation 24 hours after removal of the patches by the subject and also on Tuesday and Thursday and 48 hours after removal of the patches on Saturday. Rest Period:14 days

	Challenge Procedure: The challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed and evaluated for dermal reactions. The test sites were re-evaluated at 48 and 96 hours. The evaluation of site was not carried at 72 hours except for one subject.
Study Group	93F, 19M; age range 18-70 years
Vehicle	None
Remarks - Method	Semi-occluded. The size of the patch area and the amount of the test substance applied were not mentioned.
RESULTS	
Remarks - Results	106/112 subjects completed the study. Six subjects discontinued study participation for reasons unrelated to the test material. No adverse responses were noted at induction and challenge.
CONCLUSION	The test substance containing the notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2009)

A.6. Skin sensitisation – human volunteers (2)

TEST SUBSTANCE	Product containing the notified chemical at 29.44%
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: The test substance was applied (Monday) and allowed to remain in direct skin contact for a period of 24 hours. Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications. Patch sites were graded for dermal irritation on Monday, Wednesday and Friday. Rest Period: 7 days (only make-up cycles were scheduled) Challenge Procedure: The challenge patches were applied to previously untreated and treated test sites. After 24 hours, the patches were removed and evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours.
Study Group	65F, 49M; age range 18 - 68 years
Vehicle	
Remarks - Method	Semi-occluded. The test substance was spread on a 2 cm × 2 cm patch.
RESULTS	
Remarks - Results	103/113 subjects completed the study. No data was acquired from 1 subject and 11 subjects during the induction and challenge phase respectively. No adverse responses were noted at induction and challenge.
CONCLUSION	The test substance containing the notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	PI (2009)

A.7. Repeat dose toxicity

TEST SUBSTANCE	Analogue 1
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.
(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 not statistically significant). 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 decrease 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 NOAEL 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 (NOAEL) 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 (1999)

A.8. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 2
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 (1992)

A.9. Genotoxicity – *in vitro*

TEST SUBSTANCE	Analogue 1
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.10. Comedogenicity

TEST SUBSTANCE Analogue 2

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 50×, 200× and 500× 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 C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.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)

C.2. Ecotoxicological Investigations

C.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)

BIBLIOGRAPHY

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA and Safford R (2008) Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. Regul. Toxicol. Pharm., 52:3-23.

Biolab SGS (1992) [Notified Chemical] *Salmonella typhimurium* Reverse Mutation Assay (Report No 92/8106 June 1992). Milan, Italy. Sponsor: Enichem Augusta Industriale (Unpublished report provided by notifier

Biolab SGS (1993) Dermal Toxicity in Rats (Report No 93/14772, December 1993). Milan, Italy. Sponsor: Enichem Augusta Industriale (Unpublished report provided by notifier).

BMG (1999) [Analogue Chemical] Ready Biodegradability-Evaluation of the Aerobic Biodegradability in an Aqueous Medium: CO_2 Evolution Test (Report No.286-99, May 1999). Schlieren, Germany, BMG Engineering Ltd. (Unpublished report submitted by the notifier).

BSL Bioservice (1999a) 28-Day Oral toxicity in Rats (Report No 980850, May 1999). Behringstrasse, Germany. Sponsor: Condea Chemie GmbH (Unpublished report provided by notifier).

BSL Bioservice (1999b) *In vitro* Mammalian Chromosome Aberration Test (Report No 980852, March 1999). Behringstrasse, Germany. Sponsor: Condea Chemie GmbH (Unpublished report provided by notifier).

CIR (2012) On the Safety Assessment of Citric acid, Inorganic Citrate Salts, and Alkyl Citrate Esters as used in Cosmetics. Cosmetic Ingredient Review. March, 2012.

CPT (1988) Primary Dermal Irritation in Rabbits, Primary Ocular Irritation in Rabbits, Acute Oral Toxicity in Rats (Study No 88262, August 1988). New Jersey, United States. Consumer Product Testing (Unpublished report provided by notifier).

CRL (2009) Repeated Insult Patch Test (Study No 141508, January 2009). New Jersey, United States. Clinical Research Laboratories, Inc.

EC (2004) Guidance Document on Dermal Absorption. European Commission DG SANCO/222/2000, rev.7; 19th March 2004, 15 pp.

IBACON (1999) Acute Toxicity [Analogue Chemical] to *Daphnia magna* in a 48-hour Immobilization Test (Project No. 3463220, April 1999) Rossdorf, Germany, Institue für Biologische analytik und consulting IBACON GmbH (Unpublished report submitted by the notifier).

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

PI (2009) Determination of the Irritating and Sensitizing Propensities of MT#2349837 on Human Skin (Report No P11 № 25481, May 2009). Pennsylvania, United States. Product Investigations, Inc.

RIVM (2010) Observations on the Methodology for Quantitative Risk Assessment of Dermal Allergens, Report 320015003/2010, National Institute for Public Health and the Environment.

SCCS (2012) Notes of Guidance for testing of Cosmetic Ingredients and Their Safety Evaluation (8th revision). European Commission - Scientific Committee on Consumer Safety.

SWA (2012) Code of Practice: Managing Risks of Hazardous Chemicals in the Workplace, Safe Work Australia, http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/managing-risks-of-hazardous-chemicals-in-the-workplace.

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS), 3rd revised edition. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >.

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS) [3rd revised edition]. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >.

US EPA (2011) Estimations Program Interface Suite™ for Microsoft® Windows, v 4.10. United States Environmental Protection Agency. Washington, DC, USA.

US EPA (2012) Estimating Toxicity of Industrial Chemicals to Aquatic Organisms Using the ECOSAR (Ecological Structure Activity Relationship) Class Program for Microsoft® Windows, v 1.11. United States Environmental Protection Agency. Washington, DC, USA.