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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Hexanoic acid, 2-ethyl, 1,2,3-propanetriyl ester (Triethylhexanoin)

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 Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by Department of Sustainability, Environment, Water, Population and Communities.

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

This Full 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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FULL PUBLIC REPORT

This assessment report is for an extension of original assessment certificate for Hexanoic acid, 2-ethyl, 1,2,3-propanetriyl ester (Triethylhexanoin). Based on the submission of new information by the extension notifier, some sections of the original assessment report have been modified. These modifications have been made under the heading 'Extension Application' in the respective sections and in section 8.

Hexanoic acid, 2-ethyl, 1,2,3-propanetriyl ester (Triethylhexanoin)

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Original Applicant for Assessment Certificate
Croda Singapore Pty Ltd trading as Croda Australia (ABN 34 088 345 457)
44-46 Mandarin Street
Villawood NSW 2163

Extension Applicant:
Coty Australia Pty Ltd (ABN 96 058 696 549)
Level 31, 1 Market Street Sydney NSW 2000

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Spectral data
Impurities
Import volume

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Melting point,
Boiling point,
Density,
Vapour pressure,
Water solubility,
Hydrolysis,
Partition coefficient,
Adsorption/ desorption,
Dissociation constant,
The listed data above were not submitted however they were estimated using modelling program

Flammability limit,
Auto ignition temperature,
Explosive properties,
Reactivity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
An application for the assessment of the notified chemical for use in therapeutic goods has been submitted to TGA.

NOTIFICATION IN OTHER COUNTRIES
Japan: ENCS (2-669)
Korea: ECL (29334)
Switzerland: "BAG T" No./"Giftklasse" : 611500/"frei"

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
Hexanoic acid, 2-ethyl, 1,2,3-propanetriyl ester

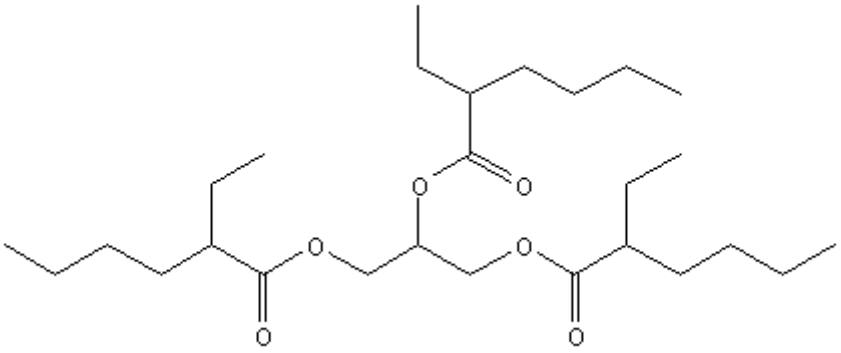
OTHER NAME(S)
Glycerol, tris (2-ethylhexanoate)
Hexanoic acid, 2-ethyl, triester with glycerol
2-ethylcaproic acid triglyceride
2-ethylhexanoic acid triglyceride
2-ethylhexyl triglyceride
Exceparl TGO
Glycerin tri(2-ethylhexanoate)
Glycerin tris(2-ethylhexanoate)
Glyceryl tri(2-ethylhexanoate)
Glyceryl tris(2-ethylhexanoate)
Hexalan
Hexalan (triglyceride)
IOTG
Nomcort TIO
Panacet 800B
RA-G 308
TIO
Trifat S308
Tris (2-ethylhexyl) glyceride
Chemical in Solaveil CT 200
Triglyceride of 2-ethylhexanoic acid
Glycerol, tris (2-ethylhexanoate)
Triglyceride of 2-ethylhexanoic acid

MARKETING NAME(S)
Estol 3609

CAS NUMBER
7360-38-5

MOLECULAR FORMULA
$C_{27}H_{50}O_6$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
470 Da

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Colourless to pale yellow, transparent oily liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	73.03 ºC	Estimated using EPIWin v12
Boiling Point	449.42ºC at 101.3 kPa	Estimated using EPIWin v12
Density	950 kg/m^3 at 25°C	MSDS
Vapour Pressure	24x10^{-9} kPa at 25ºC	Estimated using EPIWin v12
Water Solubility	1.2 ×10^{-7} g/L at 20ºC	Calculated (from fragments) using EPIWin v12
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable groups but has low water solubility.
Partition Coefficient (n-octanol/water)	log Pow = 8.98.at 20ºC	Calculated using EPIWin v12
Adsorption/Desorption	log K_{oc} = 6.45	Calculated using EPIWin v12
Dissociation Constant	Does not contain ionisable groups.	
Particle Size	N/A	Notified chemical is liquid
Flash Point	200ºC	MSDS
Autoignition Temperature	Not provided	Expected to be high based on the structure of the high flash point.
Explosive Properties	Not provided	Not expected to be explosive based on the chemical structure.

Discussion of Observed Effects

For full details of the physical-chemical properties tests please refer to Appendix A.

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

Dangerous Goods classification
Based on the available physico-chemical properties the notified chemical is not classified as a Dangerous Good according to the Australian Dangerous Goods Code (FORS, 1998).

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be introduced into Australia as a component of finished cosmetic products for personal care. It is also possible that in the future the notified chemical can be introduced into Australia as a neat substance. In this case reformulation into cosmetic products would also occur in Australia.

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

Year	*1*	*2*	*3*	*4*	*5*
Original assessment (tonne)	< 1	< 1	< 1	< 1	< 1
Extension application (tonne)	0.27	0.16	0.20	0.20	0.20
Total of original assessment and extension application (tonne)	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1

PORT OF ENTRY
Not identified at the time of notification. Possible ports of entry are: Sydney, Melbourne, Perth

IDENTITY OF MANUFACTURER/RECIPIENTS
Not available at the time of notification

TRANSPORTATION AND PACKAGING
These personal care products containing the notified chemical would be packaged in plastic and glass containers (10g-500ml) and distributed for sale. They will be transported through Australia by road.
In case of import of neat notified chemical the 200 L steel drums and/or 20 L pails will also be transported to reformulation sites by road.

USE
Specific uses have not been identified and the notifier has based this info on overseas uses. The notified chemical is intended for use as an excipient in personal care skin products such as creams, body washes, moisturisers and makeup, typically at concentrations between 1 and 15%.

Extension Application:
The notified chemical is used as a skin conditioning ingredient at up to 5% in cosmetic products.

OPERATION DESCRIPTION
The notified chemical will be introduced into Australia as a component of finished cosmetic products for personal care in plastic and glass containers (10g-500ml). These will be warehoused and transported to retail outlets, where they will be sold to consumers.
If in the future the notified chemical is introduced into Australia as a neat substance, reformulation will occur at various sites. The reformulation will include transferring of the notified chemical from the in 200 L and/or 20 L containers and mixing with various other cosmetic ingredients followed by packaging into the small 10g-500ml containers that will be distributed to consumers.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure assessment

6.1.1. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration hours/day*	*Exposure Frequency Days/year*
Delivery to wharf	10	4	40
Distribution (Storage & Transport)	100	6	240
Formulation of consumer products	200	6	240
Point of Sale	1000	6	240

Exposure Details
Transport and distribution workers are not expected to be exposed to the notified chemical except in an unlikely event of an accident and breakage of the packaging of the consumer products containing up to 46% of the notified chemical. Accidental exposure of transport and distribution workers is also unlikely in the case of import and distribution of neat notified chemical. In case of such accidental exposure, main routes of exposure would be dermal and ocular. However, the likelihood of such an accidental exposure is minimal.

In case of import of neat notified chemical for reformulation into consumer products, dermal and

ocular exposure of workers involved in reformulation may occur during transfer of the notified chemical (> 95% purity) from the drums and pails in to the mixing vessel. However, this exposure is expected to be low due to the likely automated process and PPE used by the workers.

Dermal and ocular exposure to the notified chemical in the neat form and in formulated products is possible for workers involved in quality control during sampling and testing of finished products. This exposure is also likely to be low as these workers are expected to wear laboratory coats, safety glasses and rubber gloves.

Sales workers and beauticians may experience frequent dermal and ocular exposure to the notified chemical if involved in the demonstration of products containing the notified chemical to the consumers. The extent of this exposure is likely to be comparable to the exposure of the consumers that would use the same products.

Overall, the exposure of formulators and transport workers to the notified chemical is expected to be low. However, beauticians are likely to have frequent dermal contact with cosmetic products containing the notified chemical particularly applying creams and moisturisers on consumers.

6.1.2. Public exposure

Public exposure to the notified chemical is expected to be widespread and frequent through a daily use of personal care products containing the notified chemical typically at concentrations between 1 and 15%.

The principal route of exposure is dermal, with deliberate application over the skin. Eye exposure is also possible during the use and application of the face and body skin products. Oral exposure is likely only through use of lipstick products. Oral exposure through use of other type of cosmetic consumer products is unlikely and only possible in case of accidental ingestion.

Potential systemic exposure to the notified chemical through typical consumer use of moisturising body lotions, and moisturising body lotions containing secondary sunscreens are calculated below:

Based on body lotion use:
Use Level 8 g per use x 1 applications/day 8 g/day
Dermal Exposure 8 g/day x 15% (conc. of chemical) 1.2 g/day
Absorption[a] 10% 0.12 g/day
Systemic exposure (0.12 g/day) / 60 kg bw 2 mg/kg bw/day

Or

Use Level 8 g per use x 1 applications/day 8 g/day
Dermal Exposure 8 g/day x 5% (conc. of chemical) 0.6g/day
Absorption[a] 10% 0.06 g/day
Systemic exposure (0.06 g/day) / 60 kg bw 1 mg/kg bw/day

^Based on sunscreen lotion use:
Use Level estimated as 18 g/day
Dermal Exposure 18 g/day x 15% (conc. of chemical) 2.7 g/day
Absorption[b] 5% 0.135g/day
Systemic exposure (0.135 g/day) / 60 kg bw 2.25 mg/kg bw/day

Or
Use Level estimated as 18 g/day
Dermal Exposure 18 g/day x 5% (conc. of chemical) 0.9 g/day
Absorption[b] 5% 0.045 g/day
Systemic exposure (0.045 g/day) / 60 kg bw 0.75 mg/kg bw/day

[a] and [b] vary as absorption of the notified chemical in the context of cosmetic formulation varies. The absorption of the notified chemical for moisturising lotions is likely to be higher from that for the sunscreen lotions as they are formulated to moisturise and enhance absorption into the skin, while the sunscreen lotions are formulated to retain the UV filters on the surface of the skin for maximal protection. This approach is consistent with the Notes of Guidance by the SCCNFP (2003) for the testing of cosmetic ingredients and their safety evaluation which states that when considering dermal absorption it is important to know whether the formulation can affect the

bioavailability of one of its compounds (discussed in more detail in sections 6.2 and 6.3.2)

^ Lotions with sunscreens may be covered by the NICNAS's Interim Arrangements for Regulating Cosmetic Products and are currently subject to NICNAS's Cosmetic Guidelines. Once the cosmetic reform is underpinned by legislation these products will be subject to NICNAS legislative requirements.

6.2. Human health effects assessment

Limited toxicity testing data were submitted for the notified chemical.
Based on these tests, the notified substance is not mutagenic to bacteria and does not cause chromosome aberrations in human cells in vitro.

Endpoint	*Result and Assessment Conclusion*
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro Mammalian Chromosome Aberration Test	non genotoxic

Majority of the toxicological information relating to the notification was provided in a form of report, Cosmetic Ingredient Review, on glyceryl triesters used in the cosmetic industry (CIR, 2001). The notified chemical is a triglyceride ester of 2-ethylcaproic acid that is often referred to as Trioctanon in the dictionaries of cosmetic ingredients (RIFM name). The same RIFM name is also used for the triglyceride ester of octanoic (caprylic) acid, which has the same molecular formula but different structure with linear C_8 chain in the acid moiety of the ester.

In the introduction of the report (CIR 2001), the authors recognise the differences between the notified chemical (referred to as Trioctanoin) and Tricaprylin. However, in a number of studies summarized in the CIR report that refer to Trioctanoin the identity of the tested material could not be clearly attributed to the notified chemical. This is because the original studies cite SIGMA Chemicals as the source for the test material, however SIGMA Chemicals currently only has Glyceryl Trioctanoate or Tricaprylin with CAS number 538-23-8 in their catalogue. In other original studies, summarized in the CIR report under the entry for Trioctanoin, the test material is clearly associated with CAS number 538-23-8 i.e. Tricaprylin even though the name Trioctanoin is used.

Considering the uncertainty about the identity of the tested material in the studies summarized in CIR 2001, only limited conclusions about the toxicity of the notified chemical can be made for this assessment.

Toxicokinetics, metabolism and distribution.

Ingested triglycerides are metabolised to monoglycerides, free fatty acids and glycerol, all of which are absorbed in the intestinal mucosa and undergo further metabolism. Medium chain triglycerides - MCT (C_8-C_{10}) such as the notified chemical, appear to have relatively rapid metabolism and elimination from blood and tissues compared to long chain triglycerides- LCT (C_{16}-C_{18}) (CIR 2001).

In humans, in a clinical assessment, [^{13}C]-Trioctanoin was administered orally to five normal term neonates and five growing preterm infants. The peak for ^{13}C in CO_2 appearance was between 120 to 240 minutes post administration in preterm infants and between 90 and 180 minutes post administration in full term infants. Oxidation rates for [^{13}C]-Trioctanoin were similar in preterm infants and normal neonates. Study results indicate that Trioctanoin is efficiently utilised in the neonatal period of humans as latter in life (CIR 2001).

Dermal absorption of the notified chemical has not been tested. The notifier has argued that the absorption of the notified chemical is likely to be 5%, based on the three times higher molecular weight of the notified chemical (470 kD) relative to the likely metabolite 2-ethylhexanol (130 kD) for which absorption has been determined to be 5% in Fischer 344 rats (Deisinger et al, 1994). In addition, the estimated log K_{ow} for the notified chemical is 8, indicating high hydrophobicity.

Absorption has been tested using full thickness mouse skin in vitro for Triolein, which has a similar glyceryl ester structure to the notified chemical but has significantly higher molecular weigh of 885 kD, as it is a long chain triglyceride of oleic acid (C_{18}). The absorption of Triolein varied from 0.2% to 4.7% depending on the components of the receptor fluid. Absorption was greatest in the presence of bovine serum albumin in the phosphate buffered saline/antibiotic mixture (CIR 2001).

According to the ECB Technical Guidance Document on dermal absorption (ECB 2004), in the absence of dermal absorption studies on the chemical, a default of 100% dermal absorption is used. However,

10% dermal absorption can be used for chemicals with Mw > 500 and Kow < -1 or > 4. Considering that the molecular weight of the notified chemical is close to 500 kD and the data demonstrating 5% absorption for the likely metabolite 2-ethylhexanol (Mw=130 kD; Kow = 2.73) and the structurally similar LCT triglyceride Troiolein (MW=885; Kow likely to be high due to the long aliphatic chain of the oleic acid) the absorption of the notified chemical is estimated to be between 5% and 10%.

Acute toxicity.

The acute oral toxicity of Trioctanoin (a.k.a. Glycerol Tris(2-Ethylhexanoate)) was evaluated to be low with LD50 > 50mL/kg. This is based on a study using 10 male, Ichikawaken mice treated with a dose of 50ml (unspecified concentration) of notified chemical per kg body weight. Suppression of spontaneous movement was observed immediately after test substance administration, this was described as slight on day 1 and gradual recovery followed. Some excretion of the administered dose was observed 20-30 minutes later. At 1 to 2 hours post administration, the hair appeared completely wet, this returned to normal. No mortalities were observed.

Other oral toxicity study with the similar triglyceride of octanoic acid, Tricaprylin (in unspecified strain of mice) showed very low toxicity with LD50 > 30g/kg bw and in the absence of any clinical signs. Acute subcutaneous toxicity for this trigliceride has also been determined in mice and rats and was found to be low with minimal lethal dose of > 27.8 g/kg bw.

Irritation and Sensitisation.

Based on the summary of the studies presented in the CIR report (CIR 2001) the notified chemical was not irritating to skin and eyes and has no skin sensitising potential.
Studies included Draize ocular irritation test and primary skin irritation test with undiluted Trioctanoin in rabbits. No irritation reactions were reported in both studies. Skin sensitisation potential was examined by Magnusson and Kligman test in guinea pigs using 1% intradermal and 100% topical induction followed by 25% topical challenge with Trioctanoin. In this test a slight response was observed in two guinea pigs during the first challenge but no reactions were noted during the second challenge.
The skin irritation and sensitisation potential of Trioctanoin has also been examined in humans volunteers and found to be negative (no details of protocols were provided).

Repeated Dose Toxicity (sub acute, sub chronic, chronic).

No studies of the sub chronic toxicity of the notified chemical are available. Long term effects of the notified chemical were examined through carcinogenicity and reproductive toxicity studies.
Chronic oral studies with the similar chemical Tricaprylin demonstrated few effects including lesions of the kidneys, mycoradium and the aorta when Wistar rats were dosed with up to 10 ml/kg (CIR, 2001).

Carcinogenicity

No studies aimed at determining the carcinogenic potential of the notified chemical are available. However, in a few studies examining the carcinogenic potential of number of other chemicals Trioctanoin has been used as a vehicle or background control. The results from almost all studies summarized in the CIR 2001 indicated that the tested material has carcinogenic potential in hamsters and rabbits.

In only one of the studies where Trioctanoin was used in a preliminary study to evaluate the background incidence level of development of mammary tumours in the offspring of pregnant rats treated with 1ml/kg bw of trioctanoin intraperitoneally on gestation days 16 and 17, the percentage of mammary tumours in treated and untreated female offspring was 43% and 29%, respectively. The significance of this result is not clear.

In addition it should be noted that in majority of the studies it could not be clearly determined whether the test material was the notified chemical or Tricaprylin.

Based on the results summarized in the CIR report there is no sufficient evidence to classify the notified (or the tested chemical) as carcinogenic.

Reproductive and Developmental toxicity.

Developmental toxicity of Trioctanoin was examined in CD-1 mice. Time-mated mice were treated orally with 4750 mg/kg bw/day (LD10 determined in a preliminary study with non mated mice) on gestation day 6 to 13. Litter size, birth weight and neonatal growth and survival to postnatal day 3 were recorded as indices of potential developmental toxicity. The proportion of survivors that delivered at least one liveborn pup was also compared to the corn oil control group. Study results indicated no significant differences in any of the parameters analysed (CIR, 2001).

In another study Trioctanoin was used as a vehicle control in a teratogenicity study aimed to examine the relationship of genetic factors with the effects of a known teratogen. The effects were monitored in five different strains of mice. Animals were dosed intraperitoneally on days 8-12 of gestation. Various kinds of eye abnormalities were observed in 6.2% of 291 control foetuses of the five strains studied. However, no untreated-control group or historical control data were used for comparative purposes (CIR, 2001). (Note: Identity of trioctanoin in this study could not be confirmed).

Trioctanoin was also used as a vehicle control in a sperm abnormality test. Ten male control mice received an intraperitoneal injection of 0.25 ml trioctanoin 0.05 g/kg of Benzo[α] pyrene (known reproductive toxicant and mutagen) daily for 5 days and sperm from caudae epididymides analysed. The percentage abnormal sperm in 500 sperm per animal was determined to be 4.5% $\pm$ 1.7% and 5.8% $\pm$ 2.2% in two experiments compared to 19.7% $\pm$ 16.6 for the Benzo[α] pyrene dosed similarly. No untreated controls or historical data were used for comparative purposes (CIR, 2001). (Note: Identity of trioctanoin could not be confirmed).

Based on the studies described above there is not sufficient evidence to classify the notified chemical as reproductive toxicant.

Related hazards

Metabolites

The primary metabolite of the notified chemical, along with glycerol and monoglycerides, is 2-ethyllhexanoic acid (CAS No 149-57-5) which is classified as hazardous, Reproductive toxicant Category 3 with R63 at concentrations $\geq$ 5%, under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). 2-ethyllhexanoic acid is also classified as reproductive toxicant category 3 in EU.

IUCLID dataset and SIDS dossier are available for 2-ethyllhexanoic acid. The studies summarized in this data sets indicate that 2-ethyllhexanoic acid is not mutagenic in bacterial tests, but it is clastogenic in SCE assays in CHO cells and in human lymphocytes. However, it does not induce UDS in transformed mouse lymphocyte cell line.

The studies relating to developmental and reproductive toxicity indicate that the observed adverse effects in these studies seem to be found at high doses and at maternal toxicity levels.

The studies related to developmental toxicity in rabbits indicate a lower maternal NOEL of 25/mg/kg bw/day, and developmental NOEL of 250 mg/kg bw/day with no significant effects on the foetal viability, growth or morphology.

In rats a maternal a NOAEL as low as 250 mg/kg bw/day was reported and a foetal NOEL as low as 100 mg/kg bw/day with significant increase in skeletal malformations in the foetuses.

In the absence of adequate data on the chronic, developmental and reproductive toxicity of the notified chemical and considering the reproductive toxicity potential of its metabolites, a NOAEL of 100 mg/kg bw/day was established for the notified chemical.

Classification of the notified chemical

Based on the available data the notified chemical cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Regulatory status overseas

The notified chemical is listed on the EU EINECS inventory under the name Propane-1,2,3-triyl 2-ethylhexanoate. The notified chemical is not listed in the Annex I of Directive 67/548/EEC. It is also

not listed in a priority list (as foreseen under Council Regulation (EEC) No 793/93 on the evaluation and control of the risks of existing substances.

IUCLID & OECD Chemical Data Sheets and Export Files Information is not available in EU for the notified chemical. The notified chemical is not on the OECD HPV list.

The notified chemical has not been the subject of individual SCCNFP opinions. However the SCCNFP committee recognizes the correction of the INCI names of ethylhexyl derivatives as one of the six priorities for the first INCI list update (SCCNFP, 2003).

The notified chemical is listed on TSCA (Flag P – A commenced PMN substance).

TGA has assessed the notified chemical for use in topical products and has approved its use at concentrations $\leq$ 5% in products for skin application only.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

The worst case scenarios include dermal, ocular and inhalation exposure of transport workers in case of accident if raw material containing the notified chemical (> 95 % purity) is imported in Australia. In such a case there will be a risk of skin and eye irritation. However, this situation is unlikely.

In case of import of the notified chemical as raw material, dermal, ocular and inhalation exposure to maximum of 95% of the notified chemical is possible for workers involved formulation and quality control testing of consumer products. However, exposure is expected to be minimal due to the likely automated process and the PPE used by the workers (described in detail in section 6.1.1.). Considering the low exposure and the controlled use of the notified chemical, the risk of adverse effects for formulators and workers involved in quality control testing is low.

The risk for the workers involved in packaging of the finished consumer products that may have dermal and ocular exposure to the notified chemical is acceptable as exposure is expected to be low due to use of PPE such as safety glasses and gloves for skin protection.

Sales workers can have frequent dermal and ocular exposure to the notified chemical if involved in demonstration of the products containing the notified chemical. The level of exposure and the risk of adverse effects for this category of workers is likely to be comparable to that of consumers using the same products.

Overall, the exposure of workers to the notified chemical is expected to be low.

The risk form exposure to the notified chemical for beauticians is expected to be similar to that of the public discussed in the following section.

6.3.2. Public health

Public exposure to the notified chemical is expected to be widespread and frequent through a daily use of personal care products containing the notified chemical typically at concentrations between 1 and 15%.

The risk of local adverse effect to the skin and eyes is low due to the non-irritating and non-sensitising nature of the notified chemical. However, the risk of adverse effects from systemic exposure to the notified chemical cannot be excluded for all types of products.

In the worst case scenario, the potential systemic exposure to the notified chemical through use of moisturising body lotions and body lotions with secondary sunscreens containing 15% of the notified chemical is estimated to be 2 mg/kg bw/day and 2.25 mg/kg bw/day, respectively. The absorption of the notified chemical for moisturising lotions is likely to be higher from that for the sunscreen lotions as they are formulated to moisturise and enhance absorption into the skin, while the sunscreen lotions are formulated to retain the UV filters on the surface of the skin for maximal protection. The SCCNFPs Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCNFP, 2003) states that when considering dermal absorption it is important to know whether the formulation can affect the bioavailability of one of its compounds. Ingredients can be added to formulations in order to facilitate dermal absorption of other compounds. The SCCNFP also notes that a number of factors play a key role in this process, including the lipophicility of the compounds, the thickness and composition of the stratum corneum at the body site, the duration of exposure, the amount of topically applied product, the concentration of the compounds considered and occlusion. The CIR report (CIR,

2001) states that Triolein and Tricaprylin can enhance the absorption of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetics. Therefore it is possible that formulations containing Trioctanoin may have enhanced absorption.

Considering the estimated exposure for the use of moisturising body lotions and body lotions with secondary sunscreens containing 15% of the notified chemical and NOAEL of 100 mg/kg bw/day the MOE is calculated to be 50 and 44.4, respectively. Therefore the risk of adverse effects from the use of topical products containing 15% of the notified chemical is not acceptable.

Potential systemic exposure to the notified chemical through use of moisturising body lotions and body lotions with secondary sunscreens containing 5% of the notified chemical is estimated to be 0.66 mg/kg bw/day and 0.75 mg/kg bw/day, respectively. In this case the MOE for the use of individual topical products containing 5% of the notified chemical is greater than 100 i.e. 151 and 131, for use of moisturising body lotions and body lotions with secondary sunscreens, respectively. Therefore the risk of the use of these types of products containing 5% of the notified chemical is acceptable. However, it should be noted that the consumers may use both types of products in conjunction and caution should be exercised in formulating products containing the notified chemical that may enhance dermal absorption.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is not manufactured in Australia but is imported as finished products. The potential also exists for notified chemical to be reformulated in Australia into consumer cosmetic products.

During reformulation, losses of the notified chemical will be attributed to spills, equipment washing and imported container residue. It is estimated that the worst case scenario of waste of the notified substance generated during reformulation is:
Spills: 1% of import volume (up to 10 kg per annum) likely to be disposed of to landfill.
Import container residues: 1% of import volume (up to 10 kg per annum) likely to be disposed of to landfill.
Equipment wash water: 1.5% of import volume (up to 15 kg per annum) likely to be disposed of to sewer.

RELEASE OF CHEMICAL FROM USE

It is estimated that 1% of finished product containing the notified substance will remain in the "empty" end-use container. This is expected to be disposed of to landfill. Assuming the scenario where all of the notified substance (< 1 tonne) is imported as a formulation and assuming no retention by skin, it is presumed that 99% (< 990 kg per annum) of the total (all of the applied product) will ultimately enter the sewer through washing. This is likely to occur throughout Australia.

RELEASE OF CHEMICAL FROM DISPOSAL

Public use of the product will result in disposal of the product to sewers during washing. The chemical is likely to be disposed of to landfill from occupational spills. Any chemical remaining in the container will be disposed of to landfill as domestic waste.

7.1.2 Environmental fate

The notified chemical is readily biodegradable (see appendix C). The chemical is unlikely to bioaccumulate due to its ready biodegradability. It is likely that the notified chemical will readily undergo abiotic and biotic degradation to form oxides of carbon and water. In landfill the notified chemical is unlikely to be mobile and is likely to undergo in-situ degradation to landfill gases including methane, oxides of carbon; and water vapour.

7.1.3 Predicted Environmental Concentration (PEC)

Assuming a worst case scenario where none of the chemical degrades or is adsorbed to sludge then the PEC may be calculated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1000	kg/year
Proportion expected to be released to sewer	~99%	
Annual quantity of chemical released to sewer	< 990	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.71	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP	0%	
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	< 0.66	µg/L
PEC - Ocean:	< 0.07	µg/L

7.2. Environmental effects assessment

No ecotoxicity tests were submitted and this is not required for a Limited notification. The following data were submitted with the MSDS.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	EC50 ≥ 100 mg/L	□ractically non toxic
Inhibition of Bacterial Respiration (*Pseudomonas putida*)	EC50 ≥ 100 mg/L	Non-inhibitory

7.2.1 Predicted No-Effect Concentration

Ecotoxicity data were available for one trophic level (fish). Although this data was not supported by a test result, an indicative PNEC may be calculated.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment			
			µg/L
Assessment Factor	1000		
Mitigation Factor		1.00	
PNEC:			100*

7.3. Environmental risk assessment

Insert the Risk Quotient Table (PEC/PNEC)

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.66	100*	< 0.01*
Q - Ocean:	0.07	100*	< 0.01*

* Indicative value only as no test data was provided.

The data provided indicates that the risk to the aquatic environment is acceptable. Even allowing greater toxicity to fish than that reported in the MSDS (eg. due to purity of test substance, not the most sensitive fish species tested etc.) there is an adequate safety margin to show that the risk is acceptable. Further, the notified chemical is likely to adhere to sewage sludge and rapidly degrade, thereby reducing the risk to the aquatic environment.

8. RISK ASSESSMENT AND RECOMMENDATIONS RELATING TO EXTENSION APPLICATION

The notified chemical is used in end use product for the public at up to 5% as in the original assessment. Therefore, the proposed use, introduction volume and fate of the notified chemical will not change significantly under the proposed extension. The circumstances in the extension application are not expected to impact on the original human health and environmental risk assessment.

9. CONCLUSIONS – SUMMARY OF RISK ASSESSMENT FOR THE ENVIRONMENT AND HUMAN HEALTH

9.1. Hazard classification

Based on the available data the notified chemical cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

9.2. Human health risk assessment

9.2.1. Occupational health and safety

Under the conditions of the occupational settings described, the risk to workers is considered to be acceptable.

9.2.2. Public health

When used in the proposed manner at concentrations $\leq$ 5% the risk to the public is considered to be acceptable.

9.3. Environmental risk assessment

On the basis of the PEC/PNEC ratio:

The chemical is not considered to pose a risk to the environment based on its reported use pattern.

10. MATERIAL SAFETY DATA SHEET

The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS and is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant. The MSDS was found to be in accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003).

Extension Application:
The extension applicant has provided an MSDS for the notified chemical and for a product containing the notified chemical. The accuracy of the information on these MSDS remains the responsibility of the extension applicant.

11. RECOMMENDATIONS

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as formulated into final products:
  - Use in well ventilated areas

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Overalls, Protective gloves, Protective goggles for formulators
  - Gloves for workers using end products (eg beauticians)

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)], workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Public Health

- The following measures should be taken by formulators of cosmetic products to minimise public exposure to the notified chemical:
  - The concentration of the notified chemical in the products for dermal application should not exceed 5%.
  - Formulations of products containing the notified chemical should avoid components that would significantly facilitate absorption.

Environment

Disposal

- The notified chemical should be disposed of by landfill or to sewer.

12. 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 must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if

- the importation volume exceeds one tonne per annum notified chemical; or
- if the chemical is to be introduced at concentration > 5% in cosmetic products. In the case that secondary notification is required, provision of toxicological data with regard to the dermal absorption and reproductive toxicity may be required.

or

(2) Under Section 64(2) of the Act; if

- the use of the chemical has changed from a component of skin products for topical application or a conditioning ingredient in cosmetic products, or is likely to change significantly;
- if 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.
- if any regulatory action concerning the notified chemical occurs in other jurisdictions.

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

APPENDIX A: PHYSICO-CHEMICAL PROPERTIES

No studies related to physico chemical properties were provided

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 fraction from Aroclor 1254 activated Wistar Rat liver (3% and 10% in two tests)
Concentration Range in Main Test	a) With metabolic activation: 50 to 5000 µg/plate b) Without metabolic activation: 50 to 5000 µg/plate
Vehicle	DMSO
Remarks - Method	GLP standards compliance report included. *S. typhimurium* TA102 or *E. Coli WP2* that would detect crosslinking mutagens were not included. Solvent control and positive controls 2-nitrofluorene, N-Ethyl-N'-nitro-N-nitrosoguanidine and 9-aminoacridine were used in the absence of metaboloic activation. 2-aminoanthracine was used as positive control in the presence of metabolic activation

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	Not determined	5000 reported only in preliminary test	no
Test 2		Not determined		
Present				
Test 1	> 5000	Not determined	5000 reported only in preliminary test	no
Test 2		Not determined		

CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	HRC (1990a)

B.2. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 fraction from Aroclor 1254 activated Wistar Rat liver (5%)
Vehicle	Ethanol
Remarks - Method	Positive controls: Without metabolic activation: Ethylmethane sulph750 µg/mL With metabolic activation: Cyclophosphamide 20 µg/mL

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	(range tested 7.5 to 4000) 500*, 1000*, 2000*, 4000*	24h	64h
Test 2	Not performed		
Present			
Test 1	(range tested 7.5 to 4000) 500*, 1000*, 2000*, 4000*	24h	64h
Test 2	Not performed		

*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	No preliminary test done	no		no
Test 2		Not performed		
Present				
Test 1	No preliminary test done	61% at 4000		* (see remarks)
Test 2		Not performed		

* As determined from the mitotic index

Remarks - Results

Statistically significant ($p < 0.05$) increase in % mean cells with aberrations was observed, 1.5% (mostly acentric fragments) compared to 0% in the solvent control. This result was not considered to be indicative of clastogenic changes as it was only observed at this concentration and did not appear to be concentration dependent and the value falls within the historic negative controls. The positive control in the same experiment induced significantly higher number of aberrant cells (16%).

CONCLUSION

The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

HRC (1990b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

ENVIRONMENTAL FATE

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Secondary Effluent from an unacclimatised activated sludge plant at "URL North"
Exposure Period	28 Days
Auxiliary Solvent	None specified.
Analytical Monitoring	CO_2 analyser.
Remarks - Method	Multiple vessels for the test substance containing the inoculum were prepared. Analysis of CO_2 in the headspace and liquid medium as well as dissolved inorganic carbon (DIC) were analysed at intervals on a single vessel and a control. At the conclusion of the test the remaining five vessels were analysed. The degradation was determined by comparing the total inorganic carbon (DIC + CO_2 in headspace) in the test substance with the control. A reference substance (sodium benzoate) was also run. Temperature 17-24°C.

RESULTS

Test substance		*<Reference Substance>*	
Day	*% Degradation*	*Day*	*% Degradation*
3	-4.0	3	54.5
7	-3.6	7	86.0
10	35.5	10	92.7
14	48.2	14	95.0
28	73.7	28	96.9

Remarks - Results	No remarkable observations. 95% confidence limits 70.2-78.8%
CONCLUSION	The notified chemical is readily biodegradable.
TEST FACILITY	Unilever 1994

BIBLIOGRAPHY

CIR (2001). Final report on the safety assessment of trilaurin, triarachidin, tribehenin, tricaprin, tricaprylin, trierucin, triheptanoin, triheptylundecanoin, triisononanoin, triisopalmitin, triisostearin, trilinolein, trimyristin, trioctanoin, triolein, tripalmitin, tripalmitolein, triricinolein, tristearin, triundecanoin, glyceryl triacetyl hydroxystearate, glyceryl triacetyl ricinoleate, and glyceryl stearate diacetate. Cosmetic Ingredient Review. International Journal of Toxicology. 20 (Suppl. 4): 61-94.

Deisigner et al, (1994) Metabolism of 2-ethylhexanol administered orally and dermally to the famale Fischer 344 rat. Xenobiotica 24(5) 429-440

ECB (2003) Technical guidance document (TGD) in support of Commission Directive
93/67/EEC on risk assessment for new notified substances. European Commission, Part1, pp 1–303 (http://ecb.jrc.it/technical-guidance-document/guidance/wrkdoc20_rev_en.pdf).

ECB (2004) Guidance document on dermal absorption. European Commission, pp 1–15 (ECB (2004) Guidance document on dermal absorption. European Commission, pp 1–15).

EPIsuite (2004). Estimation program interface suite (v.12). Office of Pollution, Prevention and Toxics. US Environmental Protection Agency. EPIsuite (2004). Estimation program interface suite (v.12). Office of Pollution, Prevention and Toxics. US Environmental Protection Agency

FORS (Federal Office of Road Safety) (1998) Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG code), 6th Edition, Canberra, Australian Government Publishing Service

HRC (1990a) Glyceryl Trioctanoate: Bacterial Mutation Assay (KA 890852; 20 June 1990) Huntingdon Research Centre Ltd., England (unpublished)

HRC (1990b) Glyceryl Trioctanoate: Metaphase chromosome analysis of human lymphocytes cultured in vitro. (KC 890853; 19 September 1990) Huntingdon Research Centre Ltd., England (unpublished)

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

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

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

SCCNFP (2003) Notes of guidance for the testing of cosmetic ingredients and their safety evaluation 5th revision adopted by the SCCNFP during the plenary meeting 27 October 2003. SCCNFP/0690/03 Final

United Nations (2003) Globally Harmonised System of Classification and Labelling of Chemicals (GHS). United Nations Economic Commission for Europe (UN/ECE), New York and Geneva.

Unilever (1994) Comparison of the Ready and Ultimate Biodegradability of Seven Oleochemicals, Ref: BD-SV-136, Ecotoxicology Section Unilever Research Port Sunlight Laboratory Wirral Merseyside CH62 4ZD, UK 12 July 1994 (unpublished)