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**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
(NICNAS)**

FULL PUBLIC REPORT

**Poly(oxy-1,2-ethanediyl), α -isohexadecyl- ω -hydroxy-
(INCI Name: Isoceteth-20)**

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 the 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**Poly(oxy-1,2-ethanediyl), α -isohexadecyl- ω -hydroxy-
(INCI Name: Isoceteth-20)****1. APPLICANT AND NOTIFICATION DETAILS**

APPLICANT(S)

Avon Products Pty Ltd (ABN 48 008 428 457)
120 Old Pittwater Road
Brookvale NSW 2100

NOTIFICATION CATEGORY

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)

GPC spectral Data and Molecular weight.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)

Variation to the schedule of data requirements is claimed as follows: Melting point/Boiling point, Specific Gravity/Density, Vapour pressure, Water solubility, Hydrolysis as a function of pH, Partition coefficient, Adsorption/Desorption, Dissociation constant, Particle size, Flammability limits, Auto-ignition temperature and Explosive properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)

None

NOTIFICATION IN OTHER COUNTRIES

Japan

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)

ARLASOLVE 200 (product containing the notified chemical at >60%)

CAS NUMBER

69364-63-2

CHEMICAL NAME

Poly(oxy-1,2-ethanediyl), α -isohexadecyl- ω -hydroxy-

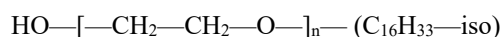
OTHER NAME(S)

ISOCETETH-20, ISOCETETH-10

MOLECULAR FORMULA

$(C_2H_4O)_n C_{16}H_{34}O$ ($C_{56}H_{114}O_{21}$ for ISOCETETH-20 where $n = 20$)

STRUCTURAL FORMULA



Where $n = 5$ to 30 .

The notified chemical is a mixture of branched chain 16 carbon alkyl alcohol ethoxylates.

MOLECULAR WEIGHT

>1000 Da

ANALYTICAL DATA

Reference IR and GPC spectra were provided.

ANALYTICAL Infrared (IR) Spectroscopy
 METHOD Major peaks at 3484, 2922, 2870, 1645, 1467, 1349, 1281, 1250, 1113, 950, 843 cm⁻¹
 Remarks The IR Spectra was done on a sample of Isoceteth-20 neat.
 TEST FACILITY In-house Avon Products Analytical Methods

3. COMPOSITION

DEGREE OF PURITY
 > 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name Oxirane
CAS No. 75-21-8 *Weight* <0.0001%
Hazardous Properties Conc>=5%: T; R45; May cause cancer, R46; May cause heritable genetic damage, R23; Toxic by inhalation, R36/37/38; Irritating to eyes, respiratory system and skin.

>=0.5%Conc<5%: R45; May cause cancer, R46; May cause heritable genetic damage, R20; Harmful by inhalation.

>=0.1%Conc<0.5%: R45; May cause cancer, R46; May cause heritable genetic damage.

CHEMICAL NAME 1,4-Dioxane
CAS No. 123-91-1 *Weight* <0.001%
Hazardous Properties Conc>=20%: Carc. Cat 3; Xn: R40; Limited evidence of a carcinogenic effect. Xi: R36/37; Irritating to eyes and respiratory system.

>=1%Conc<20%: Xn; Carc. Cat 3; R40; Limited evidence of a carcinogenic effect.

ADDITIVES/ADJUVANTS
 None

DEGRADATION PRODUCTS
 None under normal condition of use

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: White soft waxy solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	>40°C	Analogue Data (for ethoxylates)
Boiling Point	1037°C at 101.3 kPa	Calculated by QSAR
Density	1020 kg/m ³ at 45°C	Analogue Data (for ceteth-20)
Vapour Pressure	1.34 x 10 ⁻³² kPa at 25°C	Calculated by QSAR
Water Solubility	Not determined	The notified chemical is expected to be water dispersible based on its amphiphilic structure and use as an emulsifier.
Hydrolysis as a Function of pH	Not determined	The notified chemical is not expected to hydrolyse over the environmental pH range (4–9), based on the absence of readily hydrolysable functional groups
Partition Coefficient (n-octanol/water)	Not determined	The notified chemical is an emulsifier and will tend to accumulate at the

Adsorption/Desorption	Not determined	phase interface of octanol and water and/or form emulsions. The notified chemical is expected to partition to surfaces from water in the environment based on its surface activity.
Dissociation Constant	Not determined	The notified chemical contains no dissociable functions
Particle Size	Not determined	The notified chemical is a waxy solid.
Flash Point	>110°C	MSDS of the notified chemical
Flammability	Not determined	Vapour pressure anticipated to be low for flammability determination.
Explosive Properties	Not determined	Not expected to be explosive based on structure.

DISCUSSION OF PROPERTIES

Reactivity

The notified chemical is stable under normal conditions of use and compatible with other cosmetic substances under normal usage conditions.

Dangerous Goods classification

Based on the limited physical-chemical data submitted in the above table, the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However, the data above do not address all Dangerous Goods endpoints. Therefore, consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

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

The notified chemical is not manufactured in Australia and will be imported in formulated finished cosmetic products at up to 25% concentration.

The notified chemical imported at up to 25% concentration, may be reformulated in Australia into leave-on cosmetic and rinse-off cosmetic products.

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

<i>Year</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>Tonnes</i>	1	1	1	1	1

PORT OF ENTRY

Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS

Avon Products Pty Ltd.

TRANSPORTATION AND PACKAGING

The finished products containing the notified chemical will be imported in sizes up to 200 mL bottles and tubes suitable for retail sale. These bottles will be packed in cardboard cartons and these cartons will be packed to a cardboard shipper (12 cartons). The shippers will be transported in a container from the wharf to the Avon's warehouse and then transported to principal retail stores' central distribution centres by road transport. The finished products will be distributed by retail chains for retail distribution.

Larger packs of products containing the notified chemical at up to 25% may be imported to Australia. These packs will be transported in a container from the wharf to the Avon's warehouse for reformulation.

USE

The notified chemical will be used as an emulsifier or as a solubliser up to 25% in rinse off products such as shampoos, bath and shower products and up to 5% in leave on products such as skin creams and lotions for facial and body care, and antiperspirants and deodorants. The notified chemical will also be used in sprays (mousse aerosol), in lip products or oral care products at levels up to 5%.

OPERATION DESCRIPTION

The notified chemical imported in finished cosmetic products will be handled by two warehouse workers located at Avon's warehouse. The notified chemical imported for reformulation (at 25%) will be blended locally under a blending process that would be automated and occurring in a closed vessel. No atmospheric monitoring is proposed.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

<i>Category of Worker</i>	<i>Number</i>	<i>Exposure Duration (hours/day)</i>	<i>Exposure Frequency (days/year)</i>
Transport and Storage	10	4	12
Store Persons	2	4	12
End Users	300,000	8	365
Salon workers	100	1	300

EXPOSURE DETAILS

Transport, distribution and store workers are not expected to be exposed to the notified chemical except in an event of an accident.

Main routes of exposure during reformulation of products would be dermal and ocular during blending and mixing. However, the likelihood of such exposure is expected to be minimal as the blending process used would be automated and occurring in a closed vessel, and workers are expected to use PPE (safety glasses, goggles or a face shield and gloves) to minimise exposure to notified chemical.

Workers in hair and beauty salons will experience extensive dermal exposure during application of products containing the notified chemical by hand. Such professionals may use some personal protective equipment to minimise repeated exposure, and good hygiene practices are expected to be in place. Exposure of such workers is expected to be of either a similar or higher level than that experienced by consumers using products containing the notified chemical.

6.1.2. Public exposure

End-use products are also designed to be sold to consumers. Public exposure from transport, storage, reformulation or disposal is considered to be negligible. However, the general public will be repeatedly exposed to the notified chemical at up to 5% in leave-on cosmetic products and at up to 25% in rinse-off products via a number of different cosmetic products.

Public exposure to the notified chemical is expected to be widespread and frequent through daily use of personal care products containing the notified chemical. Exposure to the notified chemical will vary depending on individual use patterns. Although, the principal route of exposure will be dermal, accidental ocular exposure may also occur. Inhalation exposure is also possible if products are applied by spray. Accidental ingestion from the use of these types of products is also possible from oral care and facial products.

Public exposure to the notified chemical in Australia has been estimated using the Scientific Committee on Consumer Products' (SCCP's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation and applying the following assumptions (SCCP, 2006):

- Bodyweight of 60 kg for females;
- An individual uses all product types containing the notified chemical;
- 50% and 10% dermal absorption (refer to Sec. 6.2)

Systemic exposure from the estimated use of various types of cosmetic products are presented below:

Product type	mg/event	events/day	C (%)	RF	Daily exposure (mg/day)	*Daily systemic exposure (mg/kg bw/day)	**Daily systemic exposure (mg/kg bw/day)
Leave on products (maximum concentration = 5%)							
Body lotion	7820	1	5	1	391	3.2583	0.6517
Face cream	1540	1	5	1	77	0.6417	0.1283
General purpose cream	1200	2	5	1	120	1.00	0.2000
Rinse off products (maximum concentration = 25%)							
		1-2 (1 used in calc.)					
Facial cleansers	4060	calc.)	25	0.01	10.15	0.0846	0.0169
Make up remover	2500	2	25	0.1	125	1.0417	0.2083
Shower gel	5000	2	25	0.01	25	0.2083	0.0417
Shampoo	10460	1	25	0.01	26.15	0.2179	0.0436
Hair conditioner	14000	0.28	25	0.01	9.8	0.0817	0.0163
Hair styling products	5000	2	25	0.1	250	2.0833	0.4167

C = maximum intended concentration; RF = retention factor; Daily exposure = mg/event x events/day x C(%) x RF; Daily systemic exposure = daily exposure x dermal absorption (*50% or **10%) /bw (60 kg)

The above exposure estimates are calculated using the maximum concentration levels intended to use in different product types. As no confirmative dermal absorption data are available for the notified chemical, systemic exposure was estimated using 50% (HERA 2009) and 10% dermal absorption (CIR Tentative Amended Report Sep 2010), however dermal absorption may vary with the ingredients in cosmetic formulations and therefore, this may not be the worst case if penetration enhancers are present.

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of acute oral toxicity study can be found in Appendix B.

Endpoint	Result and Assessment Conclusion
Rat, acute oral toxicity	LD50 = 9700 mg/kg bw; low toxicity
Rabbit, skin irritation*	mild to moderately irritating
Rabbit, eye irritation*	moderately irritating

*Full studies were not available for these endpoints.

Use of Analogue Data in Human Health effects Assessment

Only limited toxicological data were provided for the notified chemical. Therefore, analogue data were used for human health effects assessment. As all toxicology information was not available for the closest analogue (C₁₆ branched chain), a range of analogues were chosen for human health effects assessment, such as Ceteths (linear C₁₆), Ceteareths (C₁₆-C₁₈), Steareths (C₁₈) and Laureths (C₁₂) and others:

Chemical Name	CAS Number	Structure	Analogue Alkyl chain carbon number
Ceteths	9004-95-9	HO—[—CH ₂ —CH ₂ —O—] _n —(CH ₂) ₁₅ —CH ₃	C ₁₆

Cetareths	68439-49-6	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{15-17}\text{---CH}_3$	C ₁₆₋₁₈
C ₁₅₋₁₆	Not available	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{14-15}\text{---CH}_3$	C ₁₅₋₁₆
C ₁₄₋₁₅ EO7	Not available	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{13-14}\text{---CH}_3$	C ₁₄₋₁₅
Stearths	9005-00-9	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{17}\text{---CH}_3$	C ₁₈
C ₁₈ EO21	9005-00-9	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_{21}\text{---}(\text{CH}_2)_{17}\text{---CH}_3$	C ₁₈
C ₁₂₋₁₅	68131-39-5	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{11-14}\text{---CH}_3$	C ₁₂₋₁₅
Laureths	9002-92-0	$\text{HO}-(\text{---CH}_2\text{---CH}_2\text{---O---})_n\text{---}(\text{CH}_2)_{11}\text{---CH}_3$	C ₁₂

EO: Ethylene Oxide

The notified chemical C₁₆ – iso and its analogues are Alcohol Ethoxylates (AE) and also called polyethylene glycol ethers (PEGs). These are manufactured by the ethoxylation of the corresponding alcohol with a number of moles of ethylene oxide (EO) to the average polyethylene glycol chain length desired.

The PEGs in the table above are close analogues to the notified chemical C₁₆ – iso. Ceteths are the closest analogue to the isoceteths (notified chemical), as both have same chain carbon number C₁₆, the difference is that C₁₆ for ceteths are linear while isoceteths' are branched. The closest analogues after the Ceteths are provided in the above table according to their order of closeness to the notified chemical.

Toxicokinetics, metabolism and distribution.

Data is not available on toxicokinetic properties of the notified chemical. However, QSAR calculations (EPI 2009) indicated low water solubility (18×10^{-3} g/L) and a partition coefficient (log Pow) value of 1.25. The notified chemical has a molecular weight average of about 1000 Daltons and a very low vapour pressure (1.34×10^{-32} kPa). All these four factors indicate low absorption following ingestion, dermal exposure or inhalation.

Cosmetic Ingredient Review 2006 (CIR), states that, in both oral and intravenous studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human burn patients, Andersen (1993) showed that PEGs appear to be readily absorbed mainly through damaged skin.

Human & Environmental Risk Assessment (HERA, 2009) studies showed that the factor influencing the adsorption, distribution and excretion of the alcohol ethoxylates was the length of the ethoxy chain and not the degree of branching. The data also as alcohol ethoxylates showed that more is excreted via the feces and expired in air as the ethoxy chain length is increased; the data suggested that the length of the ethoxy chain may determine how the alcohol ethoxylates are distributed in the rat.

Dermal absorption

No dermal absorption study is available for the notified chemical.

However, the skin penetration of a range of alcohol ethoxylates which were applied in 1% solutions was evaluated after a series of wash and rinse procedures (HERA 2009). Considerable proportions of the administered dose penetrated the skin. Shorter chained ethoxylates were absorbed more readily than longer ones.

¹⁴C-labelled C₁₂₋₁₅EO6 and C₁₂₋₁₅EO7 were applied orally and dermally to rats to evaluate the intake (absorption) and excretion in rats. The label was either in the hydroxyl-bearing carbon or the carbon of the alkyl group. The orally dosed material was absorbed quickly and extensively (>75% of the dose). The percutaneous doses were absorbed slowly and incompletely (about 50% in 72 hours). In most of the experiments about half of the ¹⁴C that was absorbed by either route was excreted promptly in the urine; smaller amounts appeared in the faeces and expired air. Much of the ¹⁴C in the faeces probably resulted from biliary excretion. The greatest amount of radioactivity was found in faeces, urine and expired air, whereas very little radioactivity remained in tissues [Drotman, 1980 (HERA, 2009)].

In rats, alcohol ethoxylates are readily absorbed in the gastrointestinal tract (*i.e.*, oral absorption has been estimated to be >75%) and rapidly excreted via the urine and faeces after oral application. The alkyl chain length appears to have an impact on the metabolism. Alcohol Ethoxylates with longer alkyl chains are excreted at a higher proportion into expired air and less in urine. Also, ethoxy chain length impacts the proportions excreted via the urine, the faeces and the expired air with more being excreted via the faeces and expired in the air with longer ethoxy chain length (HERA, 2009).

The same trends were observed when alcohol ethoxylates were administered dermally, with the only difference being that adsorption was slower and less of the total administered compound was absorbed.

When dermal absorption data are not available under the Scientific Committee on Consumer Products' (SCCP's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCP, 2006), a dermal absorption value of 100% is recommended as a worst case scenario. Alcohol ethoxylates analogues have shown approximately 50% dermal absorption (HERA, 2009).

In a later CIR report provided by the notifier ("Tentative Amended Report" Alkyl PEG Ethers as used in Cosmetics, 10 September 2010), some specific information on dermal absorption of analogues was noted. A percutaneous absorption trend data for 4 hour measurements on hairless mice series of Laureths, showed a decrease of dermal absorptions from 22.9 % to 2.1% with the increase of ethylene oxide units in Laureths from 1 to 10. The report contains a number of other animal and human dermal absorption studies. A study in rats with C12-15 PEG ethers containing 6 to 7 ethylene oxide units showed approximately 50% absorption by 72 hours. Human absorption data on Laureth-9 showed 17.6%-5.3% absorption up to 24 hours. The report states that the short chain ethoxylates were absorbed more readily than the long chain ethoxylates. As Isoceteth-20 has longer chain length than Laureths, a 10% dermal absorption was considered appropriate to use in the quantitative risk assessment.

Acute toxicity.

The notified chemical has low acute oral toxicity, with LD50 value of 9700 mg/kg bw (7800 – 12000 mg/kg bw in males and females rats).

As no acute dermal or inhalation toxicity studies were provided for the notified chemical, analogue data were used for these endpoints.

Endpoints	Analogues		
	Ceteths	Laureths	Alcohol Ethoxylate (C ₁₅₋₁₆)
Acute dermal (Rats)	-	Laureth -9 LD50 >2000 mg/kg bw low toxicity	The acute LD50 value of a 10% w/v solution in water as a single dose was greater than 800 mg/kg bw in rats . There were no deaths or signs of toxicity observed at this low concentration.
Acute inhalation	No treatment –related changes were noted after repeated 10 minute exposure to 9.6 mg/L	-	-
Reference	CIR 2006	HERA 2009	HERA 2009

Alcohol ethoxylates were shown to have a low order of acute dermal toxicity in the rat and rabbit (LD50 > 800 or > 2000 mg/kg bw in rats). There was no relationship between compound structure and dermal toxicity. Therefore, based on the analogue data, the notified chemical is likely to have low dermal toxicity.

No acute inhalation toxicity data were available for the selected analogues. However, treatment related changes were not noted after 10 minutes repeated exposure to 9.6 mg/L of ceteths. In general, alcohol ethoxylates are also considered to be of low acute inhalation toxicity to rats with LC50 values exceeding the saturated vapour concentration in air. Acute toxic thresholds were reached only when animals were exposed to the undiluted test chemical in form of a respirable mist or aerosol.

Irritation and Sensitisation.

Skin Irritation

A skin irritation study (April 1970) with 100% notified chemical, evaluated according to a Draize classification, has been provided. According to this study, the notified chemical is a mild to moderate skin irritant to the rabbit. The full study is not available.

A report on a skin irritation study conducted on 204 people in a closed patch test with 100% notified chemical, was provided (dated 6 April 1977). A patch was applied for 72 hours over an unstated amount of notified chemical and then the skin was observed daily for 10 days. At 10-14 days, a second application was made. The report concluded that the notified chemical was unlikely to cause skin irritation or skin sensitisation in humans. The full study is not available.

Based on these study reports, the notified chemical is expected to be a mild to moderate skin irritant.

In a 90 day repeat dose dermal toxicity study of Alcohol Ethoxylates C₉₋₁₁ EO6, dry and flaky skin was noted at the 10% and 25% concentrations (Gingell and Lu 1991, HERA 2009).

Eye Irritation

An eye irritation study (April 1970) with 100% notified chemical, evaluated according to the method of Kay & Calandra, has been provided. According to this study, the notified chemical is a moderate irritant to the rabbit eye. The full study is not available.

An eye irritation study (April 1977) with 50% notified chemical in water, evaluated according to the method of Kay & Calandra, has also been provided. According to this study, the notified chemical is a moderate irritant to the rabbit eye. The full study is not available.

Based on these studies, the notified chemical is expected to be a moderate eye irritant at 50% and 100% concentration. As the study details are not provided, the severity of the irritation effects are not known.

Skin Sensitisation

No data are available for the notified chemical. However, analogue data on Steareths and other Alcohol Ethoxylates are available.

Endpoint	Analogues		
	Steareths	C ₁₂₋₁₅ EO3	C ₁₈ EO21
Skin sensitisation	Steareth-20 at up to 60% in water and in cosmetic formulations was neither an irritant nor a sensitizer and was not phototoxic to human skin. Steareths-20 at 60% in water SIPT test with 200 subjects did not cause skin irritation, not a primary irritant or a skin sensitizer. At 1.5% in a moisture lotion (RIPT) test with 189 subjects was not an allergic contact sensitizer.	2% of the test substance did not cause skin sensitization in guinea pigs in Magnusson-Kligman test.	10% w/v emulsion of the test sample in de-ionized water did not elicit any sensitization response in guinea pigs in Magnusson-Kligman test
Results	Not a skin sensitizer	Not a skin sensitizer	Not a skin sensitizer
Reference	CIR 2006	HERA 2009	HERA 2009

The notified chemical is unlikely to be a skin sensitizer, based on the above analogue data.

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

A repeat dose toxicity study for the notified chemical or the close analogues was not available.

In a 90 day repeat dose dermal toxicity study of Alcohol Ethoxylates C₉₋₁₁ EO6, 10 rats per sex per group were treated with 1%, 10% and 25% of C₉₋₁₁ EO6. Treated animal showed no significant compound related effects. However, dry and flaky skin was noted at the 10% and 25% concentration. Relative kidney weights were increased in both sexes at 25% treatment level, but there were no histological lesions. The NOAEL was determined to be 10% concentration, which reflects a dose of approximately 80 mg/kg bw/day (Gingell and Lu, 1991, HERA, 2009). HERA report states that shorter chain alcohol ethoxylates are absorbed via the dermal route more readily than long chain alcohol ethoxylates and therefore 80 mg/kg bw/day dermal NOAEL for C₁₆ branched alcohol ethoxylates may be a conservative value.

A substantial number of Alcohol Ethoxylates (AEs) of different structures with regard to the length of the alkyl chain and the degree of ethoxylation were evaluated in oral and dermal repeated dose toxicity studies (HERA 2009). The NOAEL of AEs for systemic toxicity was established to be 50 mg/kg bw/d on the basis of a scientifically sound and well conducted 2-year oral feeding study in rats with C₁₂₋₁₃EO6.5. Effects observed at the LOAEL were related to significantly elevated organ-to-body weight ratios for liver, kidney and heart. No adverse histopathological changes were observed at the LOAEL. Therefore, the established NOAEL ensures an appropriate and high level of protection which was based on a scientifically sound and well conducted 2-year rat study. Moreover, this NOAEL is consistent with the outcome of the majority of existing chronic and subchronic studies determined for further AEs most commonly used in consumer products. Only one 90-day study revealed

some minor effects at a dose level of 50 mg/kg bw/d. The study investigators did not consider these effects to be of toxicological significance and suggested a NOAEL of 50 mg/kg bw/d. For assessing the risk associated with human exposure to AEs in context of its use in laundry and cleaning products, a NOAEL of 37.5 mg/kg bw/day has been considered, adjusting for the GI tract absorption (Talmage 1994, HERA 2009).

Studies which established oral NOAELs for alcohol ethoxylates are provided below (HERA Risk Assessment of Alcohol Ethoxylates); see appendix B for details.

Test Material	C ₁₄₋₁₅ EO7	C ₁₂₋₁₅ EO7	C ₁₆₋₁₈ EO10
Study summary	90 days oral feeding at dosage level of 0, 300, 1,000, 3,000, 10,000 ppm. No adverse effects were reported at 1,000 ppm (equivalent to ca. 50 mg/kg/day). Increased relative liver weight in both sexes at 3000 and 10000ppm and Haematology effects in both sexes at 10,000 ppm and in males at 3000ppm.	90 days oral feeding at dosage level of 0, 0.03, 0.063, 0.125 , 0.25, 0.5, 1.0%. The NOAELs were established on the basis of hepatic histology at the 0.125% level, corresponding to a daily intake of 102 mg/kg bw/d.	90 days oral gavage feeding at dosage level of 0, 20, 100, 500 mg/kg/day in an application volume of 10 mL/kg bw. According to the findings, the limit of systemic compatibility was 100 mg/kg bw/d for male rats. On the basis of the observations made in this study (delayed growth of the males and damage to forestomach and kidneys in both male and female rats) a NOAEL of 100 mg/kg bw/d can be established.
Estimated NOAEL	50 mg/kg bw/d	102 mg/kg bw/d	100 mg/kg bw/d

Reference: HERA 2009

The notified chemical is a C₁₆ alkyl alcohol ethoxylate. Considering the dermal and oral NOAELs available for alcohol ethoxylates and closeness of these analogues to the notified chemical, the oral NOAEL of 100 mg/kg bw/day established for C₁₆₋₁₈EO10 was considered appropriate to use in the risk assessment.

Mutagenicity.

A Mutagenicity study for the notified chemical is not available. Various mutagenicity assays on PEGs and cetyl alcohol were negative. However, CIR Cosmetic Ingredient Report for analogue Ceteths states that Ceteth-20 was found in a spot test to enhance transposition of Tn9 in *Escherichia coli*. Phage λ::Tn9-infected cells were plated on Chloramphenicol media and one to two drops of ceteth-20 (0.1%) were placed on the plate. Chloramphenicol-resistant colonies were attributed to the transposition of Tn9 to the bacterial chromosome. This effect was not observed when palmitic acid was also added suggesting that lipid or membrane was involved in the transposition process.

Based on the above information, the notified chemical is unlikely to induce reverse gene mutations in *Salmonella typhimurium* but could enhance transposition of Tn9 in *Escherichia coli* test systems.

Carcinogenicity.

A carcinogenicity study for the notified chemical or the close analogues was not available.

There have been few studies conducted using alcohol ethoxylates. The carcinogenic potential of C₁₄₋₁₅EO7 in rats has been evaluated in a one- to two-year oral feeding study. There was no evidence to indicate that treatment related changes of a carcinogenic nature were produced in rats by repeated ingestion of 0.1, 0.5 and 1% of C₁₄₋₁₅EO7. Also, no carcinogenic effects were observed in a two-year study in which 100 Sprague-Dawley rats were fed with C₁₂₋₁₃AE6.5 up to 1% in the diet (HERA Risk Assessment of Alcohol Ethoxylates). In addition, carcinogenicity studies in which various PEGs were used as solvent controls have shown negative results.

Therefore, the notified chemical is unlikely to be carcinogenic. However, the notified chemical can contain 1,4-dioxane, a by product of ethoxylation, which is a known animal carcinogen (Kociba et al. 1974). In the CIR safety assessment of the PEG reported that cosmetic industry uses additional purification steps to remove the 1,4-dioxane residual in PEG before blending into cosmetic formulations (Elder 1983).

Health hazard classification

Based on the data submitted, the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the risk phrases:

R36: Irritating to eyes

R38: Irritating to skin

In the absence of full studies with eye irritation scores (for 50% or 100% concentrations), the notified chemical is classified as an eye irritant (R36). However, severe eye irritation effects (to classify as R41) cannot be ruled out as both 50 and 100% concentrations reported moderate eye irritation in rabbits.

Based on R36/38 hazard classification for the notified chemical, products containing $\geq 20\%$ notified chemical are eye and skin irritants.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

The main acute risks of the notified chemical is mild to moderate skin irritation and moderate eye irritation.

Dermal and ocular exposure to transport and storage workers could only occur in the event of an accident of breakage or spillage of sealed containers containing the notified chemical at up to 25% concentration.

Dermal and ocular exposure of the compounders and chemists to the raw material premixes containing up to 25% concentration of the notified chemical could occur during formulation of cosmetics. The use of PPE such as protective clothing, gloves and safety glasses and automated and closed blending processes will minimise exposure to formulation workers.

Employees in hair and beauty salons may experience dermal exposure during application of products containing the notified chemical (up to 5% in leave-on products and up to 25% in rinse-off products) by hand. The exposure of these employees would be similar or higher to that of consumers. However, the use of some personal protective equipment and good hygiene practices in place would minimise exposure. Therefore, the risk of irritation effects is not anticipated to be unacceptable.

Overall, the notified chemical in leave on and rinse off products at the specified concentrations is not expected to pose an unacceptable risk to workers under the occupational conditions described.

6.3.2. Public health

As stated above, the main acute risk associated with the notified chemical is its potential to cause eye and skin irritation. Such effects are not expected to occur at the proposed concentration of 5% in leave-on products. Therefore, the irritation risk from the use of the notified chemical in leave-on cosmetic products is not expected. However, at the proposed use concentration of up to 25 % notified chemical in rinse-off cosmetic products, eye and skin irritation effects may occur if exposed before the products are diluted with water.

The public may come into contact with the notified chemical repeatedly at up to 5% through the use of a range of leave-on cosmetic products and at up to 25% through the use of a range of rinse-off cosmetic products. Therefore, repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario, as estimated in the table of Section 6.1.2.

A NOAEL of 100 mg/kg bw/day, established in the repeat dose oral toxicity study for a closer analogue (C₁₆₋₁₈EO10: see section 6.2), was used in the estimation of MOE. In this study reversible inflammatory changes in the fore stomach have been reported at 100 mg/kg bw/day. These effects were reported as most likely due to gavage administration of an irritant concentration of the test substance.

The MOE values for the notified chemical are estimated using the following:

$$\text{MOE} = \frac{\text{Estimated NOAEL}}{\text{Estimated systemic exposure}}$$

Product type	C (%)	*Daily systemic exposure	**Daily systemic exposure	*MOE	**MOE
Leave on					
Body lotion	5	3.2583	0.6517	30.7	153.5
Face cream	5	0.6417	0.1283	155.8	779.2
General purpose cream	5	1.0000	0.2000	100.0	500.0
Total (Leave on)		4.9000	0.9800	20.4	102.0
Rinse off					
Facial cleansers (1 of 2 events)	25	0.0846	0.0169	1182.3	5911.3
Make up remover	25	1.0417	0.2083	96.0	480.0
Shower gel	25	0.2083	0.0417	480.0	2400.0
Shampoo	25	0.2179	0.0436	458.9	2294.5
Hair conditioner	25	0.0817	0.0163	1224.5	6122.4
Hair styling products	25	2.0833	0.4167	48.0	240.0
Total (Rinse off)		3.7175	0.7435	26.9	134.5
Total		8.6175	1.7235	11.6	58.0

MOEs are estimated using NOAEL of 100 mg/kg bw/day

*Using 50% dermal absorption

** Using 10% dermal absorption

MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. The MOEs are unacceptable using both 50% and 10% dermal absorption. Therefore, the concentrations of the notified chemical in leave on and rinse off products need to be reduced to have acceptable total risk (MOE ≥ 100) for public using various products containing the notified chemical simultaneously.

To have an acceptable total MOE (≥ 100), the concentration of the notified chemical in leave on products should be 3.25% and 12% in rinse off products (see table below).

Product type	C (%)	Daily exposure (mg/day)	*Daily systemic exposure (mg/kg bw/day)	**MOE
<i>Leave on</i>				
Body lotion	3.25	254.15	0.4236	236.1
Face cream	3.25	50.05	0.0834	1198.8
General purpose cream	3.25	78	0.1300	769.2
Total (Leave on)		382.2	0.6370	157.0
<i>Rinse off</i>				
Facial cleansers (1 of 2 events)	12	4.872	0.0081	12315.3
Make up remover	12	60	0.1000	1000.0
Shower gel	12	12	0.0200	5000.0
Shampoo	12	12.552	0.0209	4780.1
Hair conditioner	12	4.704	0.0078	12755.1
Hair styling products	12	120	0.2000	500.0
Total (Rinse off)		214.128	0.3569	280.2
Total		596.328	0.9939	100.6

*Using 10% dermal absorption

**Estimated using NOAEL of 100 mg/kg bw/day

These estimates are based on 10% dermal absorption. Dermal absorption may vary with the ingredients in products (eg: penetration enhancers). To have an acceptable total MOE for users of all types of cosmetic products containing the notified chemical, the concentrations in both leave-on and rinse-off products need to be reduced.

Considering the uncertainties in the NOEL selected for the quantitative risk assessment of repeated use (oral NOAELs ranging from 50-700 mg/kg bw/day for different analogues of the notified chemical and dermal NOAEL of 80 mg/kg bw/day for C₉₋₁₁ EO6) and dermal absorption % used in the estimation, NICNAS is recommending that the concentration of the notified chemical should be limited to a maximum of 3.25% in leave on products and 12% in rinse off products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be manufactured overseas and imported in finished cosmetic hair and skin products at a concentration of up to 25%. Release of the notified chemical to the environment is unlikely except in the event of a transport accident or an accidental spill during handling. Accidental spills of formulated products containing the notified chemical are expected to be physically contained and then absorbed into inert material (e.g. sand or vermiculite). The absorbed chemical will be collected into sealed containers and finally disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

As the notified chemical is used in cosmetics and personal care products such as shampoos, facial and body cleansers, skin creams etc, it is expected that effectively the entire annual import volume will be released to sewer through consumer use. A small proportion (estimated to be $\leq 2\%$) may remain as residues within the end-use containers.

RELEASE OF CHEMICAL FROM DISPOSAL

Expired wastes and residue of the notified chemical in the empty containers (1%) is likely either to share the fate of the container and be disposed of to landfill, or to be washed to sewer when containers are rinsed before recycling.

7.1.2 Environmental fate

No environmental fate data were supplied. The majority of the notified chemical is expected to be released to the sewerage system. In waste water treatment processes in sewage treatment plants (STPs), a high proportion ($\geq 90\%$) of the notified chemical is expected to be removed from influent based on several fate studies of alcohol ethoxylates in STPs (Madsen et al., 2001). The high removal efficiency is due a combination of relatively rapid biodegradation and partitioning of the notified chemical to sludge and suspended solids. The notified chemical that partitions to sludge will be removed for disposal to landfill or used on land for soil remediation. In soil, the notified chemical is expected to be degraded by abiotic and biotic processes to form water and oxides of carbon.

In surface waters, the notified chemical will partition to suspended solids and organic matter and is expected to rapidly biodegrade. Based on its surface activity, the notified chemical is not expected to bioaccumulate.

7.1.3 Predicted Environmental Concentration (PEC)

A PEC for discharge of the notified chemical to surface waters has been calculated assuming that all of the imported quantity of the chemical is discharged to sewers nation wide and that 90% removal occurs in sewage treatment plants. The details of the calculation are as follows:

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	200.0	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	90%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.065	µg/L
PEC - Ocean:	0.006	µg/L

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 5.83 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1500 kg/m³ and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.039 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated biosolids application, the concentration of notified chemical in the applied soil in 5 and 10 years may approximate 0.195 mg/kg and 0.39 mg/kg, respectively. The latter soil concentrations are likely to be a

conservative overestimate as alcohol ethoxylates are known to be ultimately degraded under aerobic conditions (Madsen et al., 2001).

7.2. Environmental effects assessment

No experimental ecotoxicity data were submitted. Algae are the aquatic organisms which appear to be most sensitive to alcohol ethoxylates with EC50 endpoints ranging from 0.05 to 50 mg/L being reported in the literature (Madsen et al., 2001). The closest analogue chemical to the notified chemical in the structures considered by Madsen et al. is a linear primary alcohol ethoxylate composed of a C₁₅ hydrophobe and 7 to 8 ethoxylate units. (i.e. C₁₅EO7-8). The 72 h EC50 for *Scenedesmus subspicatus* (now known as *Desmodesmus subspicatus*) is 0.05 mg/L (Madsen et al., 2001, p55). Hence this endpoint was used as a lower limit for the calculation of the Predicted No-Effect Concentration below. This is a conservative estimate for the notified chemical since ecotoxicity of alcohol ethoxylates is known to decrease with branching in the hydrocarbon chain and increasing ethylene oxide chain length. The higher molecular weight components of the notified chemical would therefore be expected to have lower aquatic toxicity than this analogue chemical.

The notified chemical is a mixture of homologous compounds. As there are no specific ecotoxicity endpoints for this mixture of compounds, it is not appropriate, in this case, to classify the notified chemical for acute or long-term aquatic hazards under the Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2009).

7.2.1 Predicted No-Effect Concentration

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Algae (EC50)	≥ 0.05	mg/L
Assessment Factor	100	
PNEC:	≥ 0.5	µg/L

An assessment factor of 100 has been used to derive the PNEC as the notified chemical belongs to a class of compounds that have been thoroughly investigated for ecotoxicity in aquatic species at three trophic levels.

7.3. Environmental risk assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.065	≥ 0.5	≤ 0.130
Q - Ocean	0.006	≥ 0.5	≤ 0.012

The Risk Quotients (Q = PEC/PNEC) have been calculated to be < 1 for both river and ocean compartments. This indicates the notified chemical is not expected to pose an unacceptable risk to the aquatic environment based on its reported use pattern.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available data the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] with the following risk phrases:

R36: Irritating to eyes

R38: Irritating to skin

and

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	<i>Hazard category</i>	<i>Hazard statement</i>
Skin irritation	2	Causes skin irritation
Eye irritation	2B	Causes eye irritation

Human health risk assessment

Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to the health of workers when used in the proposed manner.

When used at up to 3.25% in leave on cosmetic products and up to 12% in rinse off cosmetic products, the notified chemical is not expected to pose unacceptable risk to public.

Environmental risk assessment

On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not expected to pose a risk to the environment.

Recommendations**Regulatory Controls****Hazard Classification and Labeling**

- Safe Work Australia should consider the following hazard classification for the notified chemical:
 - Xi; R36 Irritating to eyes
 - Xi; R38 Irritating to skin
- Use the following cut-off concentrations for products/mixtures containing the notified chemical:
 - Conc. \geq 20%: R36/38

Material Safety Data Sheet

- The MSDS provided by the notifier should be amended with the addition of following risk phrases:
 - R36 – irritating to eyes.
 - R38 – irritating to skin.

Control Measures**Occupational Health and Safety**

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical at 25% concentration during formulation of products:
 - Avoid contact with skin and eyes
- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation of products:
 - *Gloves*
 - *Goggles*
 - *Cotton overalls*

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 maximum concentration of the notified chemical in rinse off cosmetic products for consumer use should not be more than 12%
- The maximum concentration of the notified chemical in leave on cosmetic products for consumer use should not be more than 3.25%

Disposal

- The notified chemical should be disposed of to landfill.
- Emergency procedures
- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification

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

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

- (1) Under Section 64(1) of the Act; if
 - the importation volume exceeds one tonne per annum notified chemical;or
- (2) Under Section 64(2) of the Act; if
 - the concentration of the chemical has increased above 3.25% in leave on cosmetic products and above 12% in rinse off cosmetic products;
 - 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.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet

The MSDS 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 MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES**Melting Point/Freezing Point** >40°C

Remarks	MSDS
Test Facility	Croda Chemicals Ltd,

Boiling Point 1037°C at 101.3 kPa

Remarks	The notified chemical is likely to decompose well below this value.
Test Facility	QSAR data (EPIv4.0)

Density ~1020 kg/m³ at 45°C

Remarks	Analogue data for Ceteth MSDS
Test Facility	Croda Chemicals Ltd,

Vapour Pressure 1.34 x 10⁻³² kPa at 25°C

Remarks	
Test Facility	QSAR data (EPIv4.0)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS**B.1. Acute toxicity – oral**

TEST SUBSTANCE Notified Chemical 100%

METHOD

Species/Strain Rats/ 8 groups of 5 M+ 5F
 Vehicle Not specified
 Remarks - Method ICI inhouse method, 14 day observation period

RESULTS

<i>Group</i>	<i>Number and Sex of Animals</i>	<i>Dose mg/kg bw</i>	<i>Mortality</i>
1	5M+5F	20,000	5/5, 5/5
2	5M+5F	15,800	5/5, 3/5
3	5M+5F	12,600	5/5, 5/5
4	5M+5F	10,000	3/5, 2/5
5	5M+5F	7,940	1/5, 2/5
6	5M+5F	6,310	1/5, 0/5
7	5M+5F	5,010	1/5, 1/5
8	5M+5F	3,980	0/5, 0/5

LD50 9700 mg/kg bw

Signs of Toxicity

Effects in Organs

Remarks - Results

No necropsy were performed
 Depression, Ataxia and diarrhoea were the only signs observed at maximum and all other levels tested except for ataxia in females at 7940 mg/kg and diarrhoea in males at 12,600 mg/kg. LRR was seen in only few rats at the 2 highest levels; Bradypnea was seen at the 3 highest levels in both sexes, ptosis was present at 15,800, 12,600, and 7,940 mg/kg in males and at 20,000, 15,800, 12,600 and 10,000 mg/kg in females. These signs were observed between 45 minutes and 3 hours after dosing. Incidental signs observed included gasping, cyanosis, lacrimation, chromodacryorrhea, epistaxis, dehydrations, unkempt appearance, cannibalism and wheezing. These signs were occurred at 24 hours or later. Survivors appeared normal between 3 and 4 days. Hodge and Sterner classification is “practically non toxic”.

CONCLUSION

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

TEST FACILITY

ICI Report, April 1977

B.2. Repeat Dose toxicity studies on analogue chemicals*

Test Material (Analogue)	Study summary	Estimated NOAEL / NOEL
C₁₂₋₁₄EO7	90 days Oral feeding at dosage level of 0, 0.03, 0.063, 0.125, 0.25, 0.5, 1.0%. The body weight gain was significantly compromised in male and female rats that were fed at doses above 0.25%. This observation was associated with marked decreases in food and water consumption of these animals. Significant increases in relative liver weights were recorded in male rats fed at the 0.5 and 1.0% dose level and in female rats fed diets containing 0.25, 0.5, and 1.0% of the surfactants. The histological examination of the liver at necropsy revealed hepatocytic enlargement, suggesting an increased liver metabolism on the basis of increased alkaline phosphatase activity at the higher dose levels. No effects have been observed on the organs of the reproductive system. The NOAELs were established on the basis of hepatic histology at the 0.125% level, corresponding to a daily intake of C ₁₂₋₁₅ EO7 of 110 mg/kg bw/d. Other changes in haematological, urinary and pathological parameters were not treatment related or occurred above the NOAEL. These studies were conducted pre-GLP and followed the principles of OECD guidelines.	110 mg/kg bw/d
C₁₂₋₁₅EO7	90 days Oral feeding at dosage level of 0, 0.03, 0.063, 0.125, 0.25, 0.5, 1.0%. The body weight gain was significantly compromised in male and female rats that were fed at doses above 0.25%. This observation was associated with marked decreases in food and water consumption of these animals. Significant increases in relative liver weights were recorded in male rats fed at the 0.5 and 1.0% dose level and in female rats fed diets containing 0.25, 0.5, and 1.0% of the surfactants. The histological examination of the liver at necropsy revealed hepatocytic enlargement, suggesting an increased liver metabolism on the basis of increased alkaline phosphatase activity at the higher dose levels. No effects have been observed on the organs of the reproductive system. The NOAELs were established on the basis of hepatic histology at the 0.125% level, corresponding to a daily intake of C ₁₂₋₁₅ EO7 of 102 mg/kg bw/d. Other changes in haematological, urinary and pathological parameters were not treatment related or occurred above the NOAEL. These studies were conducted pre-GLP and followed the principles of OECD guidelines.	102 mg/kg bw/d
C₁₄₋₁₅EO7	90 days Oral feeding at dosage level of 0, 300, 1,000, 3,000, 10,000 ppm. During the study, male and female rats (<i>i.e.</i> , 6 per dose group and 12 in the control group) were observed for general health and behaviour, body weight and food intake. At necropsy, major organs including those of the reproductive system were weighed and specified tissues were examined histologically. Terminal blood samples were taken for haematological and clinical chemical evaluations. All animals survived until their scheduled necropsy date. Significant treatment-related effects on body weight (<i>i.e.</i> , reduced mean body weights in males at 10,000 ppm and in females at 3,000 ppm), food intake (<i>i.e.</i> , reduced intake in both sexes at 10,000 ppm and at 3,000 ppm for females), organ weights (<i>i.e.</i> , increased relative liver weight in both sexes at 3,000 and 10,000ppm and in females also at 1,000 ppm; increased spleen weight in males at 10,000 ppm; clinical chemistry (<i>i.e.</i> , confined to 10,000 ppm dose groups; significantly higher urea, chloride and potassium levels in males; significantly higher urea, chloride and cholesterol levels in females) and haematology (<i>i.e.</i> , in both sexes at 10,000 ppm and in males also at 3,000 ppm increased total leukocytes and lymphocytes; females at 10,000 ppm showed depression in numbers of neutrophils, mean cell volume and mean cell haemoglobin) were identified in one or both sexes fed with dietary concentrations of 3,000 and 10,000 ppm. Histopathologically, there were no compound-related effects at any dose level. No effects were observed on the organs of the reproductive system. Minor, but statistically significant changes in liver weight, kidney weights and plasma urea concentration were recorded in female rats in the 1,000 ppm group were not of toxicological significance. Taking a conservative approach, the NOEL for C ₁₄₋₁₅ EO7 can be established at a dietary level 300 ppm (15 mg/kg/day). No adverse effects were reported at 1,000 ppm (equivalent	50 mg/kg bw/d

Test Material (Analogue)	Study summary	Estimated NOAEL / NOEL
	to ca. 50 mg/kg/day).	
C₁₄₋₁₅EO7	90 days Oral feeding at dosage level of 0, 0.1, 0.5, 1.0%, the material was fed via the diet to three groups of young albino rats each consisting of 20 males and 20 females with control group consisting of an equal number of rats. The surfactant was incorporated in the diet at concentrations of 0.1%, 0.5% and 1%. During the in-life phase, standard haematological and biochemical parameters, and complete urinalyses were performed. At 28 days, five male and five female rats from each group were sacrificed and thirty tissues from each one of them were examined. At termination of the experiment, all remaining rats were autopsied. There were no treatment-related changes in body weight, food intake, and organ weights including those of the reproductive system, clinical chemistry and haematology at the 0.1%, 0.5% or 1.0% dietary intake level. The individual mean exposure for the high level males was 700 mg/kg bw/d of C ₁₄₋₁₅ EO7. The corresponding individual mean exposure for the high level females was 785 mg/kg bw/d. As there were no treatment-related findings, the NOEL was established at the highest exposure level. This study followed the principles of OECD methodology, but was not compliant with GLP regulations.	700 mg/kg bw/d
C₁₆₋₁₈EO10	90 days Oral Gavage at dosage level of 0, 20, 100, 500 mg/kg/day in an application volume of 10 mL/kg bw. Ten male and female rats were used for each dose. Five male and female animals of groups 1, 3, and 4 were observed to determine the reversibility of possible compound-related alterations for 28-days after treatment. The highest dosage resulted in delayed growth of the male animals and caused damage to forestomach and kidneys in both male and female rats. No effects were observed on the organs of the reproductive system. Inflammatory changes in the forestomach, seen in the animals in the middle dosage range (<i>i.e.</i> , 100 mg/kg/day) were less obvious and were reversible. These effects were most likely due to the gavage administration of an irritant concentration of the test substance as similar observations were not made in the dietary studies. According to these findings, the limit of systemic compatibility for C ₁₆₋₁₈ EO10 was 100 mg/kg bw/d for male rats. On the basis of the observations made in this study, a NOAEL of 100 mg/kg bw/d can be established. The study followed the OECD guideline method 408. GLP compliance was not indicated in the study report.	100 mg/kg bw/d

* Reference HERA 2009

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