Scientific Committee on Consumer Products

SCCP

OPINION ON

Polidocanol

(Laureth-9)

The SCCP adopted this opinion at its 13th plenary meeting on 2 October 2007

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).
In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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Opinion to be cited as: Opinion of the SCCP on polidocanol (laureth-9)

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1. BACKGROUND

Polidocanol (CAS 3055-99-0) with the INCI-name laureth-9 is a polyethylene glycol ether of Lauryl alcohol, where the average value of ethylene oxide units is 9. The chemical name of polidocanol is 3,6,9,12,15,18,21,24,27-nonaoxanonatriacontan-1-ol according to ECB[1].

According to the applicant the substance is used in rinse-off products as a non-ionic emulsifier and co-surfactant, particularly in shampoos and hair conditioners in concentrations from 1-4%. It is also used in leave-on products such as body and face creams up to a concentration of 3%.

The need for a scientific opinion was raised by a Member State due to the attributed anaesthetic effect of polidocanol, which is also used in medicinal creams to treat dry and pruritic skin disorders. Concerns were stated that the use of a substance with a local-anaesthetic effect in cosmetics might lead to the inability to perceive signals of skin damage such as sunburn or inflammatory reactions so that corresponding defence/avoidance reactions do not occur[2].

2. TERMS OF REFERENCE

1. *Does SCCP consider the use of laureth-9 or polidocanol safe for consumers when used in rinse-off products at a maximum concentration of 4% or when used in leave-on products at a maximum concentration of 3% taken into account the scientific data provided?*

2. *And/or does the SCCP have any further concerns regarding the use of laureth-9 or polidocanol in cosmetic products?*

[1] ECB – European Chemicals Bureau (ECB)
[2] Added 24.09.2007

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

Polidocanol belongs to the group of alkyl polyglycol ethers, commonly called alcohol ethoxylates (AEs), and is chemically defined as an AE with an average alkyl chain of 12 to 14 carbon atoms (C_{12-14}) and an ethylene oxide chain of 9 ethylene oxide units (EO_9). AEs are manufactured commercially by the reaction of an alcohol and ethylene oxide. This reaction generates mixtures of ethoxylates of different ethylene oxide units and never a pure AE. Structurally, AEs are produced with carbon units ranging between C3 and C22 and ethoxylation degrees ranging from 3 to 20 ethylene oxide units.
For the synthesis of polidocanol, natural fatty alcohols or alkyl alcohols from mineral oils are converted with ethylene oxide. According to a Gauss distribution curve one receives a broad homologous distribution with 8, 9 and 10 ethylene oxide units (EO) which constitute between 30 to 40 % of the mixture, whereby from manufacturer to manufacturer certain variances are possible. In common cosmetic products, polidocanol is defined as Laureth-9.

3.1.1.1. Primary name and/or INCI name

Laureth-9

3.1.1.2. Chemical names

Polidocanol
Polyoxyethylene (9) Lauryl Ether
PEG-9 Lauryl Ether
Nonaoxyethylene Monododecyl Ether
Nonaethylene glycol monododecyl ether

3.1.1.3. Trade names and abbreviations

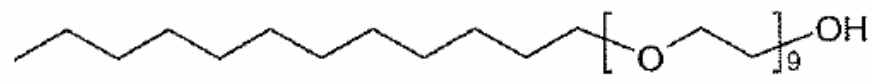
/

3.1.1.4. CAS / EINECS number

CAS: 3055-99-0
EINECS: 221-284-4

3.1.1.5. Structural formula

Due to its polymeric properties the average structural formula is shown:



3.1.1.6. Empirical formula

$C_{30}H_{62}O_{10}$ (Due to its polymeric properties the average empirical formula is shown.)

3.1.2.	Physical form

Paste or viscous liquid (appearance at 25°C)

3.1.3.	Molecular weight

The average molecular weight is approximately 580 g/mol.

3.1.4.	Purity, composition and substance codes

Concentration approx. 100 %

3.1.5.	Impurities / accompanying contaminants

/

3.1.6.	Solubility

Solubility in water (at 20°C): miscible

3.1.7.	Partition coefficient (Log P_{ow})

Log P_{ow} : /

An inherent property of surfactants is that they accumulate at the interface between two phases, which makes the accurate measurement of the P_{ow} for any surfactant not feasible.

3.1.8.	Additional physical and chemical specifications

Melting point:	15-21 °C
Boiling point:	
Flash point/Ignition temperature:	approx. 230 °C (Method: DIN 51794)
Vapour pressure:	
Density:	0.97 g/cm^3 (25 °C)
Viscosity:	
pH value (1% in water):	6.0-8.0
Refractive index:	
Cloud point	61-66 (1 g in 100 cm^3 of 10 % aqueous NaCl solution)

3.2. Function and uses

Polidocanol has been widely used in the manufacture of personal care products for over 30 years. It is most widely used in rinse off products as a non-ionic emulsifier and co-surfactant, particularly in shampoos and hair conditioners in concentrations up to 4%. It is further used in leave on products such as body and face creams at levels up to 3%.

In the submission, for the purpose of a health risk evaluation, a *worst case* approach has been chosen; it has been assumed that polidocanol is used in rinse off products at up to 10% and in general leave on products at up to 5%. Body lotions were considered to use a maximum of 2% polidocanol which, on the basis of an evaluation of the MINTEL database (MINTEL Global New Products Database, May 2007), can be considered a worst case assumption. The analysis of the MINTEL database revealed that between 2003 and 2007 (16 products were registered to use

polidocanol) the maximum usage concentration of polidocanol in body lotions is 2%, the average usage concentration is only 0.75%.

3.3. Toxicological evaluation

Polidocanol defined as Laureth-9 in common cosmetic products, describes a class of alcohol ethoxylates (AEs) with an average alkyl chain of 12 to 14 carbon atoms (C_{12-14}) and an ethylene oxide chain of 9 ethylene oxide units (EO_9). The majority of the toxicological information and human experience used to develop this human safety risk assessment dossier is based on the class of AEs covering C_{12-14} and EO_{6-12}. For certain endpoints, existing toxicological information from AEs with slightly differing alkyl chain length were also taken into account to complement and complete the picture of the potential health effects of this substance class. This approach is justified on the basis of an in-depth review and comparison of data available on the toxicokinetics, metabolism and toxicology which demonstrates that AEs with comparable structures (i.e., AEs with similar alkyl chain length and ethoxylation degree), but minor differences with branching or the length of the carbon chain or ethoxylation degree behave similarly (Fruijtier-Pölloth 2005; HERA 2006). The majority of the toxicological studies used in this health risk assessment were GLP compliant. For those which were not GLP compliant, this has been noted together with the description of the study.

3.3.1. Acute toxicity

AEs analogous to polidocanol were assessed to be of low acute oral and dermal toxicity. Generally, the acute oral LD_{50} for this class of AEs was greater than 2000 mg/kg body weight in rats, dogs and monkeys. The dermal application of this class of AEs to rat skin resulted in LD_{50} values greater than 2000 mg/kg body weight.

Table 1: Summary of acute toxicity data

Study type	Species	Endpoint	Exposure	Result	Ref.
Acute oral toxicity	Rat	LD_{50}	C_{12-13} $AE_{6.5}$ Single, neat product; Dose levels 612 to 5000 mg/kg bw	2120 mg/kg bw	39
Acute oral toxicity	Rat	LD_{50}	C_{12-13} $AE_{6.5}$ 50% solution in com oil; Dose levels 900 to 2500 mg/kg bw	2500 mg/kg bw (males) 1637 mg/kg bw (females)	44
Acute oral toxicity	Rat	LD_{50}	C_{12-15} AE_7 Neat product; Dose levels 780 to 5000 mg/kg bw	1642 mg/kg	43
Acute oral toxicity	Rat	LD_{50}	C_{12-15} AE_{11} 50% solution in corn oil; Dose levels 500 to 3160 mg/kg bw	> 2000 mg/kg bw (males) 1 000-2000 mg/kg bw (females)	23
Acute oral toxicity	Rat	LD_{50}	C_{12-14} AE_6 Single, neat product; Dose levels 5010 to 10000 mg/kg bw	4900 mg/kg bw	6
Acute oral toxicity	Beagle	LD_{50}	C_{12-13} $AE_{6.5}$	1650 mg/kg bw	1
Acute oral toxicity	Monkey	LD_{50}	C_{14-15} AE_7	6700 mg/kg bw 1 of 2 died at 10000 mg/kg bw	1
Acute dermal toxicity	Rabbit	LD_{50} Limit test	C_{12-14} AE_6 Single, neat product	>2000 mg/kg bw	36

Study type	Species	Endpoint	Exposure	Result	Ref.
Acute dermal toxicity	Rabbit	LD_{50} Limit test	C_{12-14} AE_9 Single neat product	>2000 mg/kg bw	17
Acute dermal toxicity	Rat	LD_{50}	C_{12-15} AE_7 Single, neat product	>2000 mg/kg bw	43
Acute dermal toxicity	Rat	LD50	C_{13-15} AE_7 40% suspension in corn oil dosage volume to skin 2.3 ml/kg	>920 mg/kg bw	22

3.3.1.1. Acute oral toxicity

In an acute oral toxicity study, 25% wt/wt aqueous solution of $C_{12-13}AE_{6.5}$ was administered undiluted to five albino rats of each sex at dose levels between 612 mg/kg and 5000 mg/kg. An LD50 value of 2120 mg/kg for both sexes combined was determined.

Ref.: 39

In an acute oral study, $C_{12-13}AE_{6.5}$ was administered as 50% (m/v) solution in com oil to five Fischer 344 rats of both sexes. Doses ranged between 900 and 2500 mg/kg. The LD50 was determined to be 2500 mg/kg for males and 1637 mg/kg for females.

Ref.: 44

In a further study, five rats of each sex were given doses between 700 to 5000 mg/kg undiluted $C_{12-13}AE_7$. The acute oral LD50 was determined to be 1642 mg/kg for both sexes.

Ref.: 43

In another study, dose levels of 1000 and 2000 mg/kg of C_{12-15} AE_{11} were tested in 5 male and 5 female fasted rats. The acute oral LD50 was calculated to be greater than 2000 mg/kg for males, and between 1000 and 2000 mg/kg for females. One male and four females died following exposure to a dose of 2000 mg/kg. None of the animals died after exposure to a dose of 1000 mg/kg. Decreased activity, dehydration, pilo-erection and urinary incontinence were observed at the highest dosage administered in male and female rats. No abnormalities were observed in any of the animals that were examined by necropsy at the conclusion of the study.

Ref.: 23

In a non-GLP study according to OECD 401 five rats of each sex received single doses between 5010 and 10000 mg/kg of C_{12-14} AE_6. The LD50 value was estimated to be 4900 mg/kg bw.

Ref.: 6

In non-GLP compliant acute oral studies in Beagle dogs at 1.65 g/kg of C_{12-13} $AE_{6.5}$ and monkeys at up to 6.7 g/kg of C_{14-15} AE_7 showed no effects other than emesis and diarrhoea. One of two monkeys administered 10 g/kg of C_{14-15} AE_7 died.

Ref.: 1

3.3.1.2. Acute dermal toxicity

A dermal LD_{50} of greater than 2000 mg/kg was determined for C_{12-14} AE_6 and C_{12-14} AE_9 in a limit-test. Groups of ten rats (five males and five females) were given a single dermal application of C_{12-14}.AE_6 or C_{12-14} AE_9 at a dose level of 2000 mg/kg. For both substances no deaths or signs of toxicity were observed.

Ref.: 16, 17

In another acute dermal toxicity study, five rats of each sex were given doses up to 2000 mg/kg. The acute dermal LD_{50} of $C_{12-15}AE_7$ was determined to be greater than 2000 mg/kg. The only signs of toxicity observed in both sexes were wet appearance of the fur and inflammation of the treated site.

Ref.: 43

C_{13-15} AE_{11} was applied as a 40% suspension in corn oil and administered at a maximum dosage volume of 2.3 ml/kg to the skin of twelve rats (6 male and 6 female). At the maximum dose of 920 mg/kg bodyweight, all findings were normal (i.e., no mortalities or signs of toxicity). The dermal LD50 was therefore greater than the maximum practical dose. Observations of the application site showed slight oedema in 7 of the treated animals but this dermal reaction was ameliorated by day eight.

Ref.: 22

3.3.1.3. Acute inhalation toxicity

No data

3.3.2 Irritation and corrosivity

The skin irritation potential of AEs analogous to polidocanol have been evaluated in rabbits under semi-occluded and occluded exposure conditions at concentrations from 10 to 100% for 4 and/or 24 hours. Observations were made over a period of several days after the exposure and the exposed skin sites were graded for skin irritation according to the Draize scoring scale. Under fully occluded conditions, 4 hour and 24 hour exposure to undiluted AEs resulted in moderate to severe irritation in rabbit skin. Semi-occluded 24 hour exposure to 10 to 25% of AEs resulted in no irritation. Applied undiluted, semi-occluded 24 hour exposure resulted only in mild irritating effects.

Table 2: Summary of animal skin irritation data

Study type	Species	Endpoint	Exposure	Result	Ref.
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{14-15} AE_7 Semi occluded 0.5 ml of 10, 25, 100% 4hrs	PII = 1.7 for undiluted, not irritating	47
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{12-14} AE_{10} 4hrs occlusive, neat product	PII = 4.1 moderate irritant	12
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{13} AE_6 4hrs occlusive, neat product	PII = 5.1 moderate irritant	7
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{13} $AE_{6.5}$ 4hrs occlusive, neat product	PII = 5.5 severe irritant	11
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{12-14} AE_6 4hrs occlusive, neat product	PII = 6.3 severe irritant	8
Skin irritation	Rabbit	Erythema/eschar and oedema formation	C_{14-15} AE_7 24hrs occluded, neat product	Slight to moderate erythema and moderate to severe oedema PII = 6.42 severe irritant	36

'PII' = Primary Irritation Index (up to 8; average score of the test group as a whole).

3.3.2.1. Skin irritation

In a semi occluded topical application (0.5 ml) of 10, 25 and 100% $C_{14-15}AE_7$ to rabbits for 4 hours caused irritation reactions not exceeding well-defined erythema. Resolution of the erythematous response was completed within seven days of treatment. There was a concentration-related reduction in the dermal irritation resulting from semi-occluded topical applications of 10% and 25% m/v aqueous $C_{14-15}AE_7$. PII of 1.7 was determined for undiluted $C_{14-15}AE_7$.

Ref.: 47

The dermal irritation potential of undiluted $C_{12-14}AE_{10}$, $C_{13}AE_6$, $C_{13}AE_{5-6.5}$ and $C_{12-14}AE_6$ was determined in a 4 hour exposure under fully occlusive conditions. The undiluted test materials were moderate to severe irritants with PII of 4.1, 5.1, 5.5 and 6.3. In all the studies redness extended over the application region and was accompanied with dry skin in the application area. Signs of irritation such as fissures and scaly skin persisted until the end of the observation period of 14 days.

Ref.: 7, 8, 11, 12

In a dermal irritation study, rabbits were exposed to 0.5 ml undiluted $C_{14-15}AE_7$ and occluded for 24 hours. The undiluted test material caused slight to moderate erythema and moderate to severe oedema, resulting in a PII of 6.42, a severe irritant.

Ref.: 36

Human data

The cumulative skin irritation effects of aqueous solutions of AEs analogous to polidocanol were evaluated under fully occlusive conditions in human 3-Patch application tests. Under the test conditions chosen, only slight irritation to human skin was exhibited. In a single patch test, 10% aqueous solution elicited only a slight skin irritation response.

Table 3: Summary of human skin irritation data

Study type	Duration	Endpoint	Exposure	Result	Ref.
3-Patch Application Test	4 h, 3 x week	Skin Irritation (0-4 scale)	Undiluted or 25% aqueous solution of $C_{14-15}AE_7$, occluded	None - slight irritation	25
Single-Patch Test	24 h	Skin Irritation	10% aqueous solution of $C_{12-13}AE_{6.5}$, occluded	Slight irritation	25

Ten human volunteers were exposed for 4 hours a day on 3 alternate days to undiluted or a 25% aqueous solution of $C_{14-15}AE_7$ under an occlusive patch. Only slight to negligible skin irritation was noted.

Ref.: 25

In another study, slight skin irritation was observed in 8 subjects exposed for 24 hours to an occluded patch containing a 10% aqueous solution of $C_{12-13}AE_{6.5}$.

Ref.: 25

3.3.2.2. Mucous membrane irritation

AEs structurally similar to polidocanol applied as neat or in varying concentrations of aqueous solutions, produced mild to severe irritation in rabbits' eye. Rinsing the eyes shortly after application of the test material decreased the severity of the effects. Generally, concentrations of 0.1 to 1% were non-irritating and concentrations greater than 10% produced moderate

irritation. In most cases, following exposure the eyes of the treated animals recovered a few days after exposure.

Table 4: Summary of animal eye irritation data

Study type	Species	Endpoint	Exposure	Result	Ref.
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{12-14}AE_6$ 0.1 mL neat product	EII = 27.1 moderate irritant	10
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{13}AE_{5-6.5}$ 0.1 mL neat product	EII = 44 severe irritant.	13
Eye irritation	Rabbit	Effects on comea, iris, and conjunctivae	$C_{13}AE_6$ 0.1 mL neat product	EII = 44 severe irritant	9
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{12-14}AE_{10}$ 0.1 mL neat product	EII =37 moderate to severe irritant	14
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{11-15}AE_{11}$ 0.1 mL neat product	EII=39 moderate to severe irritant	23
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{12-14}AE_7$ 0.1 mL neat product	$MAS_{unrinsed}$ = 18 MAS_{rinsed}=12	37
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{14-15}AE_{11}$ 0.1 mL neat product	$MAS_{unrinsed}$ = 30.7 MAS_{rinsed} =32	38
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{12-13}AE_{6.5}$ 0.2 mL of 0.1,1, 10 and 100% solutions	Severely irritating with 100% Moderately irritating with 10% solution 1 and 0.1% non-irritating	40
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{12-15}AE_7$ Neat and 0.5% solution	Undiluted EII = 27.8 moderate irritant 0.5% solution EII = 0.2 not irritating	21
Eye irritation	Rabbit	Effects on cornea, iris, and conjunctivae	$C_{13-15}AE_{11}$ Neat and 0.5% solution	Undiluted EII = 40.1 severe irritant 0.5%) solution, no EII only minor signs of irritation	22

'EII' = eye irritation score (from 0 to 110; Kay and Calandra, 1962).
'MAS' = maximum average irritation score

The eye irritation potential of 0.1 mL of undiluted $C_{12-14}AE_6$, $C_{13}AE_{5-6.5}$, $C_{13}AE_6$ and $C_{12-14}AE_{10}$ was evaluated. The test material was administered into the conjunctival sac of one eye of each of three rabbits over 24 hours. The other eye remained untreated to serve as a control. Initial pain reactions to the product were recorded and the eyes were examined for ocular reaction up to 21 days after the instillation of the test material using the Draize method (Draize *et al.,* 1944). The Kay and Calandra rating was used to assign an eye irritation score 'EII' from 0 to 110 (Kay and Calandra, 1962). The tested alcohol ethoxylates were found to be moderately to severely irritating to rabbits eyes. They produced eye irritation scores ranging from 27.1 to 44.2 ($C_{12-14}AE_6$, EII 27.1; $C_{13}AE_{5-6.5}$, EII 44.2; $C_{13}AE_6$, EII 44.11; and $C_{12-14}AE_{10,}$ EII 37.78). Effects were still seen for $C_{13}AE_6$ (cornea and conjunctivae in 1 animal), $C_{13}AE_{5-6.5}$ (cornea, iris and conjunctivae in 2 animals), and $C_{12-14}AE_{10}$ (cornea, iris and conjunctivae in all 3 animals) at the end of the observation period of 21 days.

Ref.: 9, 10, 13, 14

In another study, installation of 0.1 ml of undiluted $C_{12-15}AE_{11}$ into rabbit's eyes, showed signs of slight or moderate initial pain. Within 24 hours, slight to moderate redness of the conjunctivae, slight to mild Chemosis and slight to severe discharge were seen. Also slight iritis and corneal opacity were observed in one animal which was subsequently killed. Based on the observations and an EII score of 39, the test material was considered to be moderately to severely irritating.

Ref.: 23

In eye irritation studies with $C_{14-15}AE_7$ and $C_{14-15}AE_{11}$, 0.1 ml of each of the undiluted test materials was applied in the conjunctival sac of the right eye of nine animals. The treated eyes of three animals were each rinsed with 300 ml of tap water 30 seconds after treatment. The undiluted test material $C_{14-15}AE_7$ produced in unrinsed eyes a maximum average irritation score of 18 at 24 hours after treatment. In the rinsed eyes a maximum average irritation score of 12 was observed at 1 hour after treatment. The respective score at 24 hours was 7.3. Under the same conditions, $C_{14-15}AE_{11}$ produced a maximum score of 30.7 at 7 days after treatment in the unrinsed eyes, while producing a maximum score of 32 at 7 days after treatment in the rinsed eyes.

Ref.: 37, 38

The eye irritation potential of $C_{12-13}AE_{6.5}$ was evaluated at concentrations of 0.1, 1, 10 and 100% in two rabbits. A volume of 0.2 ml of the respective test solution was applied into the conjunctival sac of one eye of each rabbit. The undiluted sample was severely irritating to eyes of the rabbits 24 hours after application. Conjunctivitis and corneal opacity in both animals was observed. Due to the severity of the effects the rabbits were killed before the end of the experiment. The 10% aqueous solutions were moderately irritating causing some redness and discharge, but both eyes were normal after 7 days. The 1 and 0.1 % aqueous solutions of $C_{12-13}AE_{6.5}$ were non-irritant to the eyes of the rabbits.

Ref.: 40

The eye irritation potential of undiluted and a 0.5% aqueous solution of $C_{12-15}AE_7$, and $C_{13-15}AE_{11}$ were investigated in three rabbits. A volume of 0.1 ml of the test solutions was instilled into one eye of a rabbit. A maximum irritation score of 36.3 was determined at day 2 with undiluted $C_{12-15}AE_7$ and an eye irritation index (EII) of 27.8. The 0.5% solution resulted in a maximum irritation score of 0.7 at day 1 and an EII of 0.2. Exposure to undiluted $C_{13-15}AE_{11}$ resulted in a maximum irritation score of 53.7 determined at day 7 and an eye irritation index (EII) of 40.1.

Ref.: 21, 22

3.3.3. Skin sensitisation

The skin sensitization potential of AEs analogous to polidocanol was evaluated in two Magnusson-Kligman guinea pig maximization tests. In both studies, the investigated AEs were found to be non-sensitizing at intradermal induction concentrations of 0.05 to 0.2%, topical induction concentrations 20% to 100% and challenge concentrations up to 60%. In two Buehler tests, two AEs of the polidocanol type were not sensitizing when applied undiluted during the induction phase and challenged at concentrations of 50% in aqueous solution.

Table 5: Summary of animal skin sensitization data

Study type	Species	Endpoint	Exposure	Result	Ref.
Skin sensitization (Magnusson-Kligman)	Guinea pig	Skin sensitization	$C_{12-15}AE_7$ Intradermal induction 0.05% (m/v) in water; topical induction 20% (m/v) in water; topical challenge: 15% (m/v) in water	Not a skin sensitizer	43
Skin sensitization (Magnusson-Kligman)	Guinea Pig	Skin sensitization	$C_{14-15}AE_7$ Intradermal induction 0.2% in corn oil; Topical induction undiluted test material; Topical challenge 60% (m/v) in corn oil	Not a skin sensitizer	46
Skin sensitization (Buehler test)	Guinea pig	Skin sensitization	$C_{12-14}AE_6$ Inductions: undiluted test material Challenge: 50% in de-ionised water	Not a skin sensitizer	18
Skin sensitization (Buehler test)	Guinea Pig	Skin sensitization	$C_{12-14}AE_9$ Inductions: undiluted test material Challenge: 50% in de-ionised water	Not a skin sensitizer	19

In Magnusson and Kligman skin sensitization studies, AEs $C_{12-15}AE_7$ and $C_{14-15}AE_7$ were evaluated for their potential to cause skin sensitization. The concentrations used for induction and challenge were based on the outcome of preliminary dose range finding studies. For the main study, twenty test and ten control animals were used in both investigations. In each of the studies one of the test animals died for treatment-unrelated reasons. Only two (for $C_{12-15}AE_7$) or one out (for $C_{14-15}AE_7$) of the 19 animals of the test groups showed slight erythema 24 hours after the removal of the challenge patch. No positive responses were recorded at the 48 hour reading.

Ref.: 43, 46

The skin sensitization potential of alcohol ethoxylates $C_{12-14}AE_6$ and $C_{12-14}AE_9$ was evaluated in the non-adjuvant Buehler test protocol in guinea pigs. In both studies 20 test and 10 control animals were used. For the three dermal inductions undiluted test substance was applied. For challenge 50% of test substance in de-ionised water was used. No skin reactions were recorded for both test substance at the two readings, 24 and 48 hours after patch removal.

Ref.: 18, 19

Human data

The absence of skin sensitizing properties of AEs analogous to polidocanol were further confirmed in a series of human repeat insult patch tests (HRIPT) which evaluated formulations containing between 2.5 and 25% AEs. There was no evidence of skin sensitization in humans in any of the studies.

Table 6: Summary of human sensitization data

Study type	Duration	Endpoint	Exposure	Result	Ref.
Human Repeat Insult Patch Test (HRIPT)	3 week induction phase, 2 week rest and 24h challenge application	Skin sensitization	5, 10, 25% aqueous dilutions of $C_{12-15}AE_7$ and $C_{12-15}AE_9$	No skin sensitization	34
Human Repeat Insult Patch Test (HRIPT)	3 week induction phase, 2 week rest and 24h challenge application	Skin sensitization	15% aqueous solutions of $C_{12-13}AE_{6.5}$ and $C_{12-15}AE_{12}$	No skin sensitization	34
Human Repeat Insult Patch Test (HRIPT)	3 week induction phase, 2 week rest and 24h challenge application	Skin sensitization	1% aqueous solutions of $C_{12-13}AE_{6.5}$ and $C_{12-15}AE_9$	No skin sensitization	33
Human Repeat Insult Patch Test (HRIPT)	3 week induction phase, 2 week rest and 24h challenge application	Skin sensitization	10,15 and 20% in aerosol cream of $C_{12}AE_9$	No skin sensitization	48
Human Repeat Insult Patch Test (HRIPT)	3 week induction phase, 2 week rest and 24h challenge application	Skin sensitization	2.5% aqueous solutions of $C_{14-15}AE_7$ and $C_{12-13}AE_{6.5}$	No skin sensitization	48

$C_{12-15}AE_7$ and $C_{12-15}AE_9$ were evaluated in a Human Repeated Insult Patch Test (HRIPT) to determine their cumulative skin irritation and skin sensitizing properties. Each test material was evaluated as an aqueous solution at various concentrations of 5% w/v, 10% w/v up to 25% w/v. A patch with 0.03 ml of the test material was allowed to contact the skin for 24 hours after which time it was removed and the skin site graded for irritation. The site was then left for 24 hours after which the second patch was placed on the same site for 24 hours. This was repeated nine times followed by a 2 week rest period. After the resting period, a final 24-hour challenge patch was applied to an alternative site to determine if a sensitizing reaction to the test material occurred. During the induction phase, the patches containing the highest concentration of the test materials (i.e., 25%) caused very slight primary skin irritation. Six out of 108 subjects reacted to $C_{12-15}AE_7$ with slight erythema and 14/108 experienced dryness and itching. Similar observations were recorded for $C_{12-15}AE_9$ with 15/108 subjects exhibiting mild erythema and one test subject was recorded with well defined erythema and 26/108 persons displayed dryness and itching. At lower concentrations (i.e., 5%) fewer skin reactions were noted: 1/108 for $C_{12-15}AE_7$ and 5/108 for $C_{12-15}AE_9$ resulted in very slight erythema. The evaluation of the skin sites after challenge revealed no evidence of skin sensitization for neither of the materials. Therefore under the conditions of the test, the test materials did not possess skin sensitizing properties.

Ref.: 34

$C_{12-13}AE_{6.5}$ and $C_{12-15}AE_{12}$ were also evaluated in the HRIPT at aqueous dilutions of 5% and 15% w/v. Nine patches containing 0.03 ml of test material were placed on each of twelve subjects (i.e., per test material) over the test period of 18 days. Following a resting period of 2 weeks, a 24-hour challenge patch was applied to each of the test panellists to detect any skin sensitization potential of the test materials. At the highest concentration tested, 1/108 and 12/108 subjects developed very mild erythema and dryness and itching, following exposure to $C_{12-15}AE_{6.5}$ and similar incidences of reactions were noted with the more dilute material. None of the patients applied with the $C_{12-15}AE_{12}$ solutions developed skin reactions. There was no evidence that any of

the test materials possessed any skin sensitizing properties. The above experiments tested a series of compounds with the same C_{12-15} carbon chain length and varying ethoxylation degree from 6.5 to 12 ethoxy groups. These compounds caused only mild skin reactions even at the highest dilutions tested. The fact that those test panellists exposed to $C_{12-15}AE_{12}$ developed no or a lower cumulative irritation response compared to those exposed to $C_{12-13}AE_{6.5}$ indicates a lower irritation potential of alcohol ethoxylates with a higher ethoxylation degree.

Ref.: 34

$C_{12-13}AE_{6.5}$ and $C_{12-15}AE_9$ was tested in another HRIPT. Test materials were evaluated at a concentration of 1% w/v aqueous solutions. In the induction phase, nine patches containing the test substances were placed on each of the twelve subjects. After a resting period of 2 weeks, the test panellists were challenged with a 24 hour patch. During the induction phase, very slight primary skin irritating properties were observed for $C_{12-13}AE_{6.5}$ with one subject reacting at four time points with very slight erythema. There was no evidence of any skin sensitizing properties as a result of the challenge patch. $C_{12-15}AE_9$ did not possess any significant primary skin irritating properties and there was no evidence of any skin sensitizing properties.

Ref.: 33

$C_{12}AE_9$ tested at 10, 15 and 20% in an aerosol (foamy) cream was well tolerated in an HRIPT at all concentrations and none of the observed reactions were indicative of a skin sensitization reaction.

Ref.: 48

Volunteers wore patches containing 2.5% aqueous solutions of $C_{14-15}AE_7$ (144 subjects) and $C_{12-13}AE_{6.5}$ (176 subjects) for up to three weeks and were then subjected to a challenge test 17 days later. Skin hyper-reactivity occurred only to one subject exposed to $C_{12-13}AE_{6.5}$. However, subsequent home usage tests with formulations containing these surfactants indicated no significant skin irritation.

Ref.: 48

There are two case reports indicating that polidocanol can act as contact allergen, one with exposure being from a shampoo (Grillo et al. 2007) the other with exposure to a skin-care product (Gallo et al. 2001).

Addit. ref.: 2, 3

The evaluation of a large clinical patch test population demonstrated that the compound is an uncommon allergen, but may be relevant in elderly patients with lower leg dermatitis (Uter et al. 2000).

Addit. ref.: 6

3.3.4. Dermal / percutaneous absorption

In vitro

No data submitted.

Animals

The percutaneous absorption of ^{14}C-labelled $C_{12}AE_3$, $C_{12}AE_6$ and $C_{12}AE_{10}$ was investigated in female Colworth Wistar rats. The test compounds were applied in 1% solutions and were then evaluated following a series of wash and rinse procedures. The study results demonstrated that a

considerable proportion of the administered dose penetrated the skin. The shorter chained ethoxylates were absorbed more readily than the longer ones. The penetration of $C_{12}AE_3$ and $C_{12}AE_6$ were 4-5 µg/cm^2 rat skin after single 5 minute wash with 1% (w/v) AE solutions. Only 0.85 µg $C_{12}AE_{10}$ /cm^2 penetrated from a similar test solution applied for 5 minutes. Penetration of all three test compounds was proportional to longer durations of contact and multiple applications (e.g., highest penetration rate of 8.4 µg/cm^2 was observed after 20 minute contact to $C_{12}AE_3$.

Ref.: 55

The absorption and excretion of ^{14}C-labelled $C_{12\text{-}15}AE_6$ and $C_{12\text{-}15}AE_7$ administered dermally was investigated in Cox CD rats. In this study, a solution of 0.5 mg of AE in 0.5 ml water was applied to the back of the animals on an area of 20 cm^2 of shaved skin. The rats were restrained in stocks to keep them from licking their backs, and they were placed in metabolism cages. Samples were collected at 24, 48 and 72 hours. Approximately 50% of the dermal dose was absorbed in 72 hours. Most of the experiments demonstrated that about half of the ^{l4}C that was absorbed dermally, was excreted rapidly in the urine. The highest concentration of radioactivity was found in faeces, urine and expired air and the radioactivity found in tissues was negligible.

Ref.: 4

Humans

Human male volunteers were used to investigate the dermal penetration of $C_{12}AE_6$. A solution of 100 mg ^{14}C-labelled $C_{12}AE_6$ (as 50/50 ethanol/water solution) was applied onto the skin of the outer forearms of two male volunteers across an area of 90 cm^2. A non-occlusive metal shield was used to protect the treated areas for duration of 8 hours. The exposed outer forearms of the two volunteers were washed repeatedly to remove any remaining solution and the area was stripped 10 times by repeated applications of cellulose tape. Blood samples were taken at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 144 hours post application. Urine and faeces were collected at 0-6 hrs, 6-24 hrs and thereafter during each 24 hour period up to 144 hours. Expired air was collected continuously over the first 6 hours and after that for 15 minutes at 8, 12, 24, 30, 48 and 72 hours. The majority of the radioactive solution was removed by cleansing the application site with alcohol soaked gauze (i.e., Subject 1; 73.9% and Subject 2; 87.5%). Less than 2% (i.e., Subject 1; 1.82% and Subject 2; 1.02%) was detected in the urine and none was detected in the faeces or as CO_2. In Subject 2 low levels of activity were detected in the blood. 0.14 µg/g at 8 hours, 0.02 µg/g at 12 hours and 0.01 µg/g at 24 hours. This indicated that the majority of dermally absorbed $C_{12}AE_6$ was absorbed within the first 24 hours. Total radioactivity recovery for Subject 1 and Subject 2 was 82.4% and 94.7% respectively. The major route of elimination was through urinary excretion.

Ref.: 4

Twenty-two atopic dermatitis patients were treated with a polidocanol containing bath oil either by bathing in the diluted product or by applying the oil onto the skin for 8 h after having showered. Percutaneous penetration was quantified by measuring polidocanol blood concentrations and urinary excretion rates (Buhles & Richter 1989). The blood concentrations resulting from bath or after shower application was 0.015-0.021 µg/ml and hence more than 1000-fold lower than those possibly reached with intravenous use of polidocanol as a sclerosing agent. The calculated absorption was 0.0017 % for bath application and 0.0035% for the after-shower application

Addit. ref. #1

The calculation of the systemic availability of polidocanol for the safety evaluation is carried out using the dermal absorption rate of 2% in humans as the most realistic scenario. This view is based on the well known differences between rat and human skin penetration which

demonstrates in general, a higher permeability for rats compared to humans. This approach is also supported by a recently performed risk assessment on polidocanol by the German Federal Institute for Risk Assessment (BfR, 2003) which has also used the 2% dermal absorption rate from the Drotman study in humans.

Ref.: 2

3.3.5. Repeated dose toxicity

The subacute, subchronic and chronic toxicity of AEs analogous to polidocanol provide a coherent picture of their systemic toxicity profile demonstrating low toxicity. The no observed adverse effect level (NOAEL) for systemic toxicity was established to be 50 mg/kg bw/day based on a sound and well conducted two-year oral feeding study in rats. To allow comparison of the oral NOAEL to dermal systemically available exposure of AEs analogous to polidocanol present in consumer products, a systemic NOAEL of 37.5 mg/kg bw/d was calculated by considering a conservative oral absorption rate of 75% (i.e., 50 mg/kg bw/d x 0.75 = 37.5 mg/kg bw/d). The oral absorption rate was based on the toxicokinetic study conducted by Unilever (Unilever, 1978d). The derived systemic NOAEL of 37.5 mg/kg bw/d will be the basis for the calculation of the margin of safety (MoS).

Ref.: 55

Table 7: Summary of repeated dose toxicity

Study type	Species	Endpoint	Exposure	Result	Ref.
Subacute (21 d) oral feeding	Rat	Subacute toxicity	$C_{12-14}AE_7$ 0,0.023,0.047, 0.094, 0.188,0.375,0.75,1.0	Estimated NOAEL 502 mg/kg bw /d	50
Subacute (21 d) oral feeding	Rat	Subacute toxicity	$C_{12-15}AE_7$ 0, 0.023,0.047, 0.094, 0.188,0.375,0.75,1.0	Estimated NOAEL 459 mg/kg bw /d	51
Subacute (21 d) oral feeding	Rat	Subacute toxicity	$C_{12-15}AE_{11}$ 0,0.023,0.047,0.094, 0.188,0.375,0.75,1.0 0,	Estimated NOAEL 519 mg/kg bw /d	49
Subchronic (90 d) oral feeding	Rat	Subchronic toxicity	$C_{12-14}AE_7$ 0, 0.03, 0.063, 0.125,	Estimated NOAEL 110 mg/kg bw /d	52
Subchronic (90 d) oral feeding	Rat	Subchronic toxicity	$C_{12-15}AE_7$ 0,0.03,0.063, 0.125,0.25,0.5,1.0%	Estimated NOAEL 102 mg/kg bw /d	53
Subchronic (90 d) oral feeding	Rat	Subchronic toxicity	$C_{14-15}AE_7$ 0,300, 1000, 3000, 10000 ppm	Estimated NOAEL 50 mg/kg bw /d	41
Subchronic (90 d) oral feeding	Rat	Subchronic toxicity	$C_{14-15}AE_7$ 0., 0.1, 0.5, 1.0% i.e. 0, 1000, 5000, 10000 ppm	Estimated NOAEL 700 -785 mg/kg bw /d	28
Subchronic (90 d) oral feeding	Rabbits	Subchronic toxicity	2.5 % $C_{14-15}AE_7$	Not possible to establish as treatment effects and other factors such as disease not possible to differentiate	29
Chronic (2 years) dietary feeding study	Rat	Chronic toxicity	$C_{12-13}AE_{6.5}$ $C_{14-15}AE_7$ 0, 0.1, 0.5, 1%	NOAEL =50 mg/kg bw/d LOAEL=50 mg/kg bw/d	48
Chronic (2 year) dietary feeding study	Rat	Chronic toxicity	$C_{12-14}AE_7$ 0, 0.1, 0.5, 1%	NOAEL =162 mg/kg bw/d	26, 48

3.3.5.1. Repeated Dose (28 days) oral / dermal / inhalation toxicity

In a series of 21-day oral feeding studies AEs analogous to polidocanol were examined for repeated dose toxicity (see Table 7). The established NOAELs ranged from 459 to 519 mg/kg bw/d. At higher dose levels the organ mostly affected in these studies was the liver, indicated by increased liver weight and hepatic hypertrophy.

The repeated dose toxicity of $C_{12-14}AE_7$, $C_{12-15}AE_7$ and $C_{12-15}AE_{11}$ was evaluated in a 21-day oral toxicity study using three Colworth Wistar rats per sex per dose and 6 animals of each sex in the control group. All compounds were tested at dietary concentrations of 0%, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1.00% and 1.5%. In all studies the growth of the experimental animals was retarded at the higher doses of 0.75% to 1.5%. Changes in plasma protein concentration and organ weights (i.e., heart, liver and spleen) were associated with this effect on growth. The liver appeared to be the major target organ for these compounds. The observed changes in the liver were judged to be indicative of an adaptive response rather than a true adverse effect. On the basis of observed increases in liver weight and hepatocytic hypertrophy, the lowest observed effect level (LOEL) in all these studies was established at the 0.75% dietary level. No treatment-related effects were observed at the 0.375% dietary level leading to the establishment of the NOAEL at this exposure level, which is equivalent to a dose of about 502 mg/kg bw/d ($C_{12-14}AE_7$) 459 mg/kg bw/d ($C_{12-15}AE_7$) and 519 mg/kg bw/d ($C_{12-15}AE_{11}$).

Ref.: 49, 50, 51

3.3.5.2. Sub-chronic (90 days) oral / dermal / inhalation toxicity

In several 90-day oral subchronic studies, the NOAELs ranged between 50 and 785 mg/kg bw/d (see Table 7). At higher dose levels the investigators observed body weight depressions and in some studies elevated organ-to-body weight ratios in the liver, kidney and heart.

In a 90-day dietary feeding study using Colworth Wistar rats, $C_{12-15}AE_7$ and $C_{12-14}AE_7$ were tested at dose levels of 0%, 0.03%, 0.063%, 0.125%, 0.25%, 0.5% and 1.0% active material. In both studies, 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 test materials. 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 $C_{12-15}AE_7$ of 102 mg/kg bw/d and of $C_{12-14}AE_7$ of 110 mg/kg bw/d. Other changes in haematological, urinary and pathological parameters were not treatment-related or occurred above the NOAEL.

Ref.: 52, 53

In a 90-day oral feeding study, $C_{14-15}AE_7$ was fed to Wistar rats at dietary concentrations of 0, 300, 1,000, 3,000, and 10,000 ppm of active ingredient. During the study, male and female rats (i.e., 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 specific tissues underwent histological examination. Terminal blood samples were taken for haematological and clinical evaluations. All animals survived until their scheduled necropsy date. Significant treatment-related effects on body weight (i.e., reduced mean body weights in males at 10,000 ppm and in females at 3,000 ppm), food intake (i.e., reduced intake in both sexes at 10,000 ppm and at 3,000 ppm for females), organ weights (i.e., increased relative liver weight in both sexes at 3,000 and 10,000 ppm and in females also at 1,000 ppm; increased spleen weight in males at 10,000 ppm) clinical chemistry (i.e., 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.e., 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. Histopathology revealed no compound-related effects at any dose level. No effects were observed in 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. However, these observations were not of toxicological significance. The NOAEL for $C_{14-15}AE_7$ was established at a dietary level of 300 ppm (15 mg/kg bw/d). No adverse effects were reported at 1,000 ppm which is equivalent to 50 mg/kg bw/d.

Ref.: 41

In another 90-day feeding study, $C_{14-15}AE_7$ was fed in the diet at concentrations of 0.1%, 0.5% and 1% to three groups of young albino rats each consisting of 20 males and 20 females with a control group consisting of an equal number of rats. During the in-life phase, standard haematological and biochemical parameters, and complete urinalysis 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 processed for histological examination. At termination of the experiment, all remaining rats underwent autopsy. 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 dose level (males) was 700 mg/kg bw/d. The corresponding individual mean exposure for the high dose level (females) was 785 mg/kg bw/d. As there were no treatment-related findings, the NOAEL was established at the highest exposure level.

Ref.: 28

A 90-day dermal toxicity study in rabbits was conducted using a 2.5% aqueous solution of $C_{14-15}AE_7$. The animals (3 of each sex per treatment) received a total of 65 exposures during a 13-week treatment period. The test solution was applied 5 days a week for 6 hours at dosage levels of 2 ml/kg bw/d. Three animals of the treatment group died in the course of the study. The cause of death in all 3 animals was a result of an infectious disease (also observed in the control group) in combination with the stress produced by the treatment schedule. In the surviving animals moderate localized test compound induced dermal irritation, indicated amongst other signs by erythema and oedema, was noted in all surviving animals of both test groups during each week of treatment. A NOAEL could not be established as it was impossible to differentiate between treatment-related effects and other factors such as disease of the animals in this study, especially as only few of the animals remained at the end of the study.

Ref.: 29

3.3.5.3. Chronic (> 12 months) toxicity

In two chronic toxicity studies, no adverse effects were observed up to dose levels of 50 mg/kg bw/d (see Table 7). At higher dose levels (i.e., 250 and 500 mg/kg bw/d) reduced food consumption, elevated organ to body weight ratios and reduced body weight gain was observed.

No unusual findings of systemic toxicity were noted in a two year chronic feeding study in rats fed $C_{12-13}AE_{6.5}$ or $C_{14-15}AE_7$ the diet at levels of 0%, 0.1%, 0.5% and 1% (i.e., equals about 500 mg/kg bw/d). Reduced food consumption at the higher dose levels (i.e., 0.5 and 1% for females and 1% for males) resulted in a lower body weight gain compared to the control group. After 104 weeks, elevated organ to body weight ratios were observed for females fed with the 0.5 and 1% dose (i.e., liver, kidney and brain), females fed with the 1% dose (i.e., heart), and males fed at the 1% dose level (i.e., liver). In male rats, dose related focal myocarditis was the only pathology observed. Although this is a common spontaneous type of lesion in aging rats,

incidences were higher in the treated group than in the control group. No tumours or other treatment-related lesions were observed. On the basis of the observed relative organ weight increase at the 0.5% dietary intake level, the NOAEL can be established at the 0.1% level which is a daily intake of about 50 mg/kg bw/d.

Ref.: 48

In a second chronic oral feeding study, Charles River rats were fed with $C_{14-15}AE_7$ containing diet at dose levels of 0, 0.1, 0.5 and 1%. Dose related body weight depression in females in the upper two treatment levels and in males at the 1% dose level was due to the poor palatability of the diet. At termination, elevated organ-to-body weight ratios were noted for the liver, kidney, heart and thyroid/parathyroid glands at the highest exposure level. The only significant histopathological finding prevalent in all dose groups was a dose related increase in incidence of focal myocarditis at 12 months but not at study termination at 2 years. No other treatment-related histopathology and no increase in tumour incidence were reported. On the basis of these observations the NOAEL was established at the 0.5% level which is equivalent to a daily exposure of about 190 mg/kg bw/d for female rats and 162 mg/kg bw/d for male rats.

Ref.: 26, 48

3.3.6. Mutagenicity / Genotoxicity

AEs analogous to polidocanol were found not to be mutagenic in the Ames test or clastogenic in the chromosomal aberration test with or without metabolic activation.

Table 8: Summary of available genotoxicity data

Study type	Test system	Endpoint	Result	Ref.
Ames test	$C_{12-14}AE_6$ *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537	Mutagenicity	Not mutagenic with or without metabolic activation	20
Ames test	$C_{12-14}AE_9$ *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537	Mutagenicity	Not mutagenic with or without metabolic activation	15
Ames test	$C_{14-15}AE_7$ *S. typhimurium* strains TA98, TA 100, TA 1535, TA1537 and TA 1538 *Escherichia coli* Wp2 uvrA pKMIOl	Mutagenicity	Not mutagenic with or without metabolic activation	42, 45
Gene mutation test	$C_{14-15}AE_7$ *Saccharomyces cerevisiae*	Mutagenicity	Not mutagenic with or without metabolic activation	42
Chromosomal aberration test	$C_{14}AE_{12}$ Chinese hamster ovary cells (CHO)	Clastogenicity	Negative for the induction of chromosomal aberrations with or without metabolic activation	35

Study type	Test system	Endpoint	Result	Ref.
Chromosomal aberration test	$C_{14-15}AE_7$ Rat liver cells	Clastogenicity	Negative for the induction of chromosomal aberrations with or without metabolic activation	48
Micronucleus test	Chinese hamsters administered oral doses of $C_{13-15}AE_7$ 25% active solution at levels of 3.4 g/kg and 1.7 g/kg active ingredient	Clastogenicity	Negative	54
Micronucleus test	Chinese hamsters administered oral doses of $C_{12-14}AE_7$ 10% aqueous	Clastogenicity	Negative	56

In vitro

The mutagenic activity of the alcohol ethoxylates $C_{12-14}AE_6$ and $C_{12-14}AE_9$ was studied in the Ames plate incorporation as well as in preincubation assay. *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 were incubated to the test substances in the presence and absence of a metabolic activation system at test concentrations in the range of 1 to 5000 µg per plate. For both test substances no mutagenic activity was observed in any of the tester strain.

Ref. 15, 20

The mutagenic activity of $C_{14-15}AE_7$ was investigated in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and *Escherichia coli* WP2 uvrA pKM101. The dose levels ranged from 1 to 5000 µg/plate. The tests were conducted in triplicate both with and without the addition of a metabolizing system (i.e., Aroclor 1254 induced rat liver S9 mix). All 5 bacterial strains exhibited mutagenic response to the positive control substance. For the solvent controls the mean numbers of spontaneous revertants were in the acceptable range. Mutagenic activity of the test compound to any of the tester strains was not observed with or without metabolic activation. It was therefore concluded that under the given test conditions $C_{14-15}AE_7$ is not a bacterial mutagen.

Ref.: 42, 45

The mutagenic potential of $C_{14-15}AE_7$ was further evaluated in a *Saccharomyces cerevisiae* gene conversion assay. The assay was carried out with and without metabolic activation. It was concluded that the addition of $C_{14-15}AE_7$ to liquid suspension of *Saccharomyces cerevisiae* did not induce mitotic gene conversion in yeast.

Ref.: 42

In another study $C_{14}AE_{12}$ was tested for its ability to induce chromosome aberrations in the Chinese hamster ovary (CHO) cells cultured *in vitro* with or without metabolic activation. Medium controls, solvent controls and positive controls were run concurrently with the test compound. $C_{14}AE_{12}$ did not demonstrate an effect on cytogenetic parameters under the conditions tested, although the highest concentration resulted in cytotoxic effects.

Ref.: 35

The ability of $C_{14-15}AE_7$ to induce chromosome aberrations in rat liver cells was investigated. In slide cultures exposed to culture medium containing $C_{14-15}AE_7$ at concentrations of 10, 15, 20, and 25 µL/ml, the frequency of chromatic and chromosome aberrations did not differ significantly from that of control cultures.

Ref.: 48

In vivo

The potential of $C_{13-15}AE_7$ to induce chromosome damage in Chinese hamster bone marrow cells after an acute oral dose was evaluated in an *in vivo* cytogenetic assay. In this study, $C_{13-15}AE_7$ was administered as a 20% aqueous solution at doses of 3.4 g/kg and 1.7 g/kg active ingredient. In both cases, cyclophosphamide was used as the positive control and saline as the negative control. There were eight male and eight female animals at each dose level which were killed 24 hours after compound administration. Chromosome preparations were prepared from the bone marrow and ten slides from each animal were scored for metaphase aberrations. $C_{13-15}AE_7$ did not induce chromosome damage under the test conditions.

Ref.: 54

In a similar experiment, $C_{12-14}AE_7$ was administered as a 10% aqueous solution to male and female Chinese hamsters by oral intubation at two dose levels, 1.25 g/kg and 2.5 g/kg active ingredient. Chromosome preparations were made from the bone marrow 24 hours after administration. Metaphase divisions were scored for aberrations and there was no indication that $C_{12-14}AE_7$ damaged chromosomes under the given test conditions.

Ref.: 56

$C_{14-15}AE_7$ was administered orally to 5 male and female Tunstall Wistar rats at doses of 250, 500 and 1,000 mg/kg. Bone marrow smears were prepared 24 hours later and were processed for chromosome analysis. $C_{14-15}AE_7$ did not show any potential for clastogenicity under the given test conditions.

Ref.: 42

3.3.7. Carcinogenicity

The potential for carcinogenicity was evaluated in two-year rat chronic oral feeding studies in which rats were fed with a diet containing AEs analogous to polidocanol at doses up to 1% (500 mg/kg bw/d). There was no evidence of a dose-related increase in tumour incidence at any site and it was therefore concluded that alcohol ethoxylates were not carcinogenic under the test conditions.

Table 9: Summary of carcinogenicity data

Study type	Species	Endpoint	Exposure	Result	Ref.
Chronic (2 years) dietary feeding study	Rat	Carcinogenicity and chronic toxicity	$C_{14-15}AE_7$ 0,0.1,0.5,1%	Not carcinogenic	31
Chronic (2 years) dietary feeding study	Rat	Carcinogenicity and chronic toxicity	$C_{12-13}AE_{6.5}$ 0,0.1,0.5,1%	Not carcinogenic	48

Two year dietary toxicity study

The carcinogenic potential of $C_{14-15}AE_7$ in rats was evaluated in a one to two year oral feeding study. $C_{14-15}AE_7$ was administered at dietary levels of 0, 0.1, 0.5 and 1% to four groups of Charles River rats (i.e., 65 of each sex) for one or two years. Fifteen males and females from the control and the 0.5% dose group, 15 males and 14 females from the 0.1% dose group, and 14 males and 15 females from the 1% dose group were sacrificed after an interim of 1 year exposure. The remaining animals were treated for the 2-year period. Administration of $C_{14-15}AE_7$ for a period of 1 or 2 years did not produce any compound related changes in general behaviour and appearance. The survival rate of the test animals was comparable if not better than the controls. Females fed with 0.5% $C_{14-15}AE_7$ and males and females fed with 1% $C_{14-15}AE_7$ had significantly lower body weight gains than the control. At necropsy, no compound-related effects were observed in organ to body weight determinations. 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% $C_{14-15}AE_7$.

Ref.: 31

No carcinogenic effects were observed in a two-year study in which 100 Sprague-Dawley rats were fed with diet containing $C_{12-13}AE_{6.5}$ at doses up to 1% (i.e., 500 mg/kg bw/d). Reduced food consumption was noted at the higher dose levels (i.e., 0.5 and 1% for females and 1% for males), resulting in a lower body weight gain compared to the control group. No treatment-related histopathology was found and no increase in tumour incidence was observed. Therefore, $C_{12-13}AE_{6.5}$ is not considered to be carcinogenic.

Ref.: 48

3.3.8. Reproductive toxicity

The reproductive toxicity of AEs was investigated in two-generation feeding studies in rats. The AEs, structurally similar to polidocanol, did not cause toxicity to reproduction. Hence, the NOAEL for toxicity to reproduction was determined to be greater than 250 mg/kg bw/d. The NOAEL for maternal toxicity was determined to be 50 mg/kg bw/d. For developmental toxicity a NOAEL of greater than 50 mg/kg bw/d was established. At higher exposure levels a reduced pup body weight was observed in the second generation.

Table 10: Summary of reproduction and developmental toxicity

Study type	Species	Endpoint	Exposure	Result	Ref.
Two generation dietary feeding	Rat	Reproductive toxicity	$C_{14-15}AE7$ 0, 25, 50, 250 mg/kg bw/d	$NOAEL_{repro}$= 250 mg/kg bw/d NOEL F_1 = 50 mg/kg bw/d	30
Two generation dietary feeding	Rat	Reproductive toxicity	$C_{12}AE_6$ 0, 25, 50, 250 mg/kg bw/d	$NOAEL_{repro}$ = 250 mg/kg bw/d NOEL F_1 = 50 mg/kg bw/d	48
Two generation dietary feeding	Rabbit	Developmental toxicity	$C_{12}AE_6$ 0,50,100,200 mg/kg_bw/d	NOAEL > 50 mg/kg bw/d	48

3.3.8.1. Two generation reproduction toxicity

The reproductive toxicity of $C_{14-15}AE_7$ was evaluated in a two-generation study conducted in Charles River CD rats. One control group and six treatment groups of 50 animals (25 males and 25 females) were used in this study. Compound administration was carried out at dietary levels of 0.05%, 0.1% and 0.5% (i.e., approximately 25, 50 and 250mg/kg bw/d). Three of the treatment groups received the dietary levels of the compound throughout the study. Of the remaining three treatment groups, only the females received the compound during the 6th and 15th day of gestation. The males were not treated in these latter groups. No compound-related differences were observed between control and treatment groups in terms of fertility, gestation or viability indices. Therefore, a NOAEL for reproduction at a dietary intake level greater than 0.5% was determined which corresponds to a dose of 250 mg/kg bw/d.

Ref.: 30

The reproductive toxicity of $C_{12}AE_6$ was evaluated in a two-generation feeding study using a similar experimental design as described above. Rats were exposed in a two-generation study to the compound at dose levels of 25, 50 or 250 mg/kg bw/d. No treatment-related effects in the parents or pups on general behaviour, appearance or survival were observed. Fertility of the treated groups was comparable with the controls. The only observation was related to a reduced weight gain of parental rats and pups relative to the control at the highest dose level (i.e., 250 mg/kg bw/d). The NOAEL for reproduction was therefore set at the highest dose level which was 0.5% dietary level greater than 250 mg/kg bw/d.

Ref.: 48

Other studies

In a study with $C_{12}AE_6$, 25 female rabbits were orally administered doses of 0, 50, 100 or 200 mg/kg bw/d from day 2 to day 16 of gestation. Caesareans were performed on the 28th day of pregnancy. A definite increase in maternal toxicity, evidenced by ataxia and a slight decrease in body weight was observed at 100 and 200 mg/kg bw/d. No effects were observed for parameters such as corpora lutea, implantations, number of live foetuses and spontaneous abortions. Nine control rabbits and 31 treated rabbits died during the study. Surviving rabbits at the 200 mg/kg bw/d dose level generally showed slight losses of body weight. In seven treated and two control rabbits early deliveries were recorded. The NOAEL for this study based on the maternal toxicity was therefore assumed to be greater than 50 mg/kg bw/d level.

Ref.: 48

3.3.8.2. Teratogenicity

The reproduction and developmental toxicity of $C_{14-15}AE_7$ were evaluated in a two-generation study conducted in Charles River CD rats as described in Section 3.3.8.1. In addition, on day 13 of gestation, laparotomies were performed on a representative number of female rats from the FC generation (i.e., offspring from the 3rd mating of the F0 and F1 parental generation). The uterus of the female rats was examined for uterine abnormalities, normal implantation and resorption sites. The remaining females were sacrificed on day 21 of gestation and corpora lutea were counted and the presence and distribution of live and dead foetuses was recorded. Foetuses were removed and examined for external abnormalities, sexed and weighed. A variety of measured maternal and foetal indices differed significantly from the control group, however these differences were not dose-related and so not attributed to the test compound. Parental female rate and pups of the high dose group did not gain as much body weight as the control rats. Examination of organ weight values revealed compound-related effects were limited to increased group mean liver weights of male and female P1 generation from the 0.5% continuous feeding group at the 91-day sacrifice and increase in group mean relative liver weights of males of the 0.5% continuous feeding group of the P2 generation at the 60-day

section sacrifices. The NOAEL for maternal and developmental toxicity was established at the 50 mg/kg bw/d dose level.

Ref.: 30

The reproduction toxicity and developmental effects of $C_{12}AE_6$ was evaluated in a two-generation feeding study using a similar experimental design as described in section 3.3.8.1. Rats were exposed in a two-generation study to the compound at dose levels of 25, 50 or 250 mg/kg bw/d. No treatment-related effects in the parents or pups on general behaviour, appearance or survival were observed. Fertility of treated groups was comparable with the controls. The only observation was related to a reduced weight gain of parental rats and pups relative to the control at the highest dose level (i.e., 250 mg/kg bw/d). The NOAEL for reproduction was therefore set at the highest dose level which was 0.5% dietary level greater than 250 mg/kg bw/d. In the 0.5% dose group, there was a statistical increase in embryo lethality and soft tissue anomalies and at the 0.1% there was a statistical decrease in mean foetal liver weight. Neither of these effects was considered to be treatment-related by the authors as they showed no dose response characteristics. The NOAEL for maternal toxicity was 50 mg/kg bw/d. The NOAEL for developmental toxicity was determined to be 50 mg/kg bw/d.

Ref.: 48

3.3.9. Toxicokinetics

Animals

Pharmacokinetic studies in rats with ^{14}C-labelled AEs C_{12-15} and AE_{3-10} demonstrated that these AEs are readily absorbed in the gastrointestinal tract. It has been estimated that >75% of these AEs orally administered are rapidly absorbed and excreted via the urine and faeces. The alkyl chain length appears to have an impact on the metabolism. AEs with longer alkyl chains are excreted at a higher proportion into expired air and less in urine. AEs administered by the dermal route demonstrated incomplete absorption as half of the administered dose was absorbed in 72 hours and the major route of excretion being via the urine.

The absorption, distribution, metabolism and excretion (ADME) of three ^{14}C-labelled alcohol ethoxylates (i.e., $C_{12}AE_3$, $C_{12}AE_6$ and $C_{12}AE_{10}$) were examined in female Colworth Wistar rats following administration of the test solutions through oral intubation, intraperitoneal injection or subcutaneous injection. Following administration, the rats were placed in a metabolism chamber for 4 days during which faeces, urine and air were monitored for ^{14}C activity. The study was terminated at the end of the 4-day period. Following analysis for radioactivity in various tissues and organs, rats administered the test material via the oral and parental routes, excreted ^{14}C primarily in the urine. The recoveries were almost 100% for all routes. The relative proportions of compounds found in the urine, faeces, air and carcass did not differ with the route of application. Smaller amounts were recovered as $^{14}CO_2$ and in the faeces (see Table 11). These proportions increased with longer ethoxylate length. In conclusion, the results suggest that nearly all the absorption is from the alimentary tract. There were indications that some of the longer ethoxylate chain compounds may be excreted via the bile or excreted into the intestine by other routes. Each test substance gave rise to two distinct polar metabolites in the urine and no parent compound.

Ref.: 55

Table 11: Recoveries (%) of ^{14}C from rats administered $^{14}Ci2AEx$ via oral intubation, intraperitoneal injection or subcutaneous injection four days after administration (Unilever, 1978d)

Ethoxylate length	Urine (%)	Faeces (%)	Expired Air (%)	Carcass (%)	Total Recovery (%)
Oral					
E3 E6 E10	78.3	6.9	6.5	2.5	94.3 ± 9.2
	76.3	11.8	8.1	1.8	98.2 ±1.5
	49.8	17.4	12.4	4.5	84.2 ± 6.8
Intraperitoneal					
E3 E6 E10	84.5	2.1	6.7	1.8	95.3 ±5.8
	85,1	9.1	4.1	0.8	99.4 ±4.4
	61.5	18.2	14.2	3.2	97.1 ±3.3
Subcutaneous					
	87.5	4.4	4.3	3.7	99.8 ±4.6
	83.5	10.2	4.6	2.9	101.2 ±3.3
	61.2	19.9	11.7	4.9	97.7 ± 2.2

Ref.: 55

The absorption and excretion of ^{14}C-labelled $C_{12-15}AE_6$ and $C_{12-15}AE_7$ administered orally to Cox CD rats was investigated. More than 75% of the oral dose was absorbed rapidly. In general, most of the experiments demonstrated that about half of the ^{14}C that was absorbed orally, was excreted rapidly in the urine. The highest concentration of radioactivity was found in urine, faeces and expired air and the radioactivity found in tissues was negligible.

Ref.: 4

Humans

The metabolism and excretion of radio-labelled AEs $C_{12}AE_6$ and $C_{13}AE_6$ in humans following oral exposure was comparable to that in rats. The major route of excretion was via the urine as 75% of the radioactivity was found in the urine within the first 24 hours. Excretion via faeces and respired air was 5% and 4%, respectively.

Radio-labelled $C_{12}AE_6$ and $C_{13}AE_6$ were used to investigate absorption, distribution and excretion in human male volunteers. Treatment groups of volunteers were composed of six adult individuals. Groups were either treated with radio-labelled $C_{12}AE_6$ or $C_{13}AE_6$. Volunteers were administered 50 mg capsules containing the radio-labelled AE. Blood samples were taken at 0.5, 1, 1.5, *2,* 4, 6, 8, 12, 24, 48 and 144 hours post-application. Urine and faeces were collected at 0-6 hours, 6-24 hour and thereafter during each 24 hour period up to 144 hours. Expired air was collected continuously over the first 6 hours and after that for 15 minutes at 8, 12, 24, 30, 48 and 72 hours. Analysis of urine and faeces indicated that the majority of radioactivity was excreted via the urine (i.e., 75%) in the first 24 hours post-treatment. Faecal radioactive elimination was recorded as 5% and 4% in respired in air. The majority of the radioactivity for both $C_{12}AE_6$ and $C_{13}AE_6$ was excreted in the urine, faeces and expired air 144 hours post-treatment (i.e., 83-89%). Much lower levels were detected in the blood and remained below 1%. Human metabolism of $C_{12}AE_6$ and $C_{13}AE_6$ is similar to that of rat metabolism. Distribution and excretion of the two compounds was similar but the metabolic product of each compound was a defined function of carbon chain length. The longer carbon chain ethoxylates produced more metabolic CO_2 and less urinary elimination products.

Ref.: 4

The degradation of the ether linkage and oxidation of the alkyl chain to form lower molecular weight polyethylene glycol-like compounds and carbon dioxide and water is the major

degradation pathway of alcohol ethoxylates. The metabolism of the alkyl chain seemed to change as the alkyl chain length increased with longer alkyl chains giving rise to a higher percentage of $^{14}CO_2$ into expired air, and a lower percentage in urine. Studies with radio-labelled compounds showed that both the alkyl chain and the ethoxylate groups are sites of attack.

Ref.: 4, 48

3.3.10. Photo-induced toxicity

No data provided

3.3.10.1. Phototoxicity / photoirritation and photosensitisation

/

3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity

/

3.3.11. Human data

See other sections of the dossier [in 3.3.2.1 and Tab.3; in 3.3.3 and Tab.6; in 3.3.4 and in 3.3.9]

3.3.12. Special investigations

Two studies have investigated the possible anaesthetic properties of polidocanol, in parallel with proven local anaesthetic agents.
Leopold and Maibach (2004) have studied various non-ionic surfactants and local anaesthetics in respect of the thermal reaction of the skin. They tested Polidocanol (Laureth-9), Ceteareth-30, Oleth-5, Oleth-10 (all surfactants); also Mepivacaine-HCl, Bupivacaine-HCl, Tetracaine-HCl, Prilocaine-HCl, Lidocaine-HCl as well as two combination preparations of the anaesthetics Lidocaine-HCl/Prilocaine-HCl (1:1) and Lidocaine-HCl/Prilocaine-HCl/Tetracaine-HCl (1:1:1). All substances were tested in respect of heat and cold sensation upon application of 100 mg to an area of 3.5 x 3.5 cm^2 on the volar aspect of the forearm. The results of the studies showed that the therapeutically used anaesthetics lidocaine, prilocaine and the combination preparations had a significant effect on the sensation of heat and cold; however, the tested surfactants, including polidocanol, had a clearly lower effect or even no effect at all.

Add. Ref.: 4

The antipruritic effect of antihistamines and topical anaesthetic preparations after iontophoretic histamine irritation was studied by Weisshaar et al. (1996). They tested in 12 volunteers several local therapeutics and their basic substances, i.a. Fenistil®-Gel (Zyma, gel with dimethondene maleate), EMLA® (Astra Chemicals, crème with prilocain 2.5%, lidocain 2.5%) and Xilocain®-Salbe (Astra chemicals, crème with lidocain 5%). Most interesting in this context are the results for Optiderm® (Hermal, cream, polidocanol 3%) and Optiderm® basic formulation (Hermal, cream, no active substance). Through pre-treatment with Optiderm® the histamine-induced areas with weals, reddening and alloknesis (alloknesis = itchy skin) were significantly reduced in size compared with histamine induction without pretreatment, and the itching sensation was significantly reduced between minute 15 and minute 20. There were no significant differences between Optiderm® and its urea-containing cream basis without polidocanol. All topically applied substances, irregardless of antihistaminic or anaesthetic potential, reduced the area of alloknesis, including the placebo cream.

The authors attribute the antipruritic effect to the presence of urea in the base cream.

Add. Ref.: 7

Comment
Based on the results described above and additional considerations two expert statements arrived at the conclusion that polidocanol is not effective as a local anaesthetic on the skin. It has antipruritic properties, but this effect is different from a local anaesthetic effect and not sufficient to suppress strong itching or pain. Thus, polidocanol in cosmetic products will not mask skin symptoms and prevent people from recognizing or treating skin diseases.

Add. Ref.: 5, 8

3.3.13. Safety evaluation (including calculation of the MoS)

Exposure

Polidocanol is most widely used in rinse off products as a non-ionic emulsifier and co-surfactant, particularly in shampoos and hair conditioners in concentrations up to 4%. It is further used in leave on products such as body and face creams at levels up to 3%.

The following table summarizes the exposure to polidocanol from:

a) rinse-off products at a maximum concentration of 4% and
b) general leave-on products at a maximum concentration of 3%;

Product category	Type of cosmetic product	Quantity of product per application (g)	Frequency of product applications (use/ day)	Daily exposure to product (g/day)	Retention /partition factor (%)	Max. Conc. of polidocanol in product (%)	Exposure to polidocanol in product (g/day)
Rinse-off	Hair conditioner	14.0	0.28	3.92	1	4	**0.002**
	Shampoo	8.0	1	8.0	1	4	**0.003**
	Shower gel	5.0	2	10.0	1	4	**0.004**
Leave-on	Facial cream	0,8	2	1.6	100	3	**0.048**
	General purpose cream	1.2	2	2.4	100	3	**0.07**
	Body lotion	8.0	1	8.0	100	3	**0.24**
	Hair styling	5.0	2	10.0	10	3	**0.03**
Total exposure							**0.397**

CALCULATION OF THE MARGIN OF SAFETY

Maximum amount of ingredient applied daily			
From rinse off products	I (mg/day)	=	9
From leave on products	I (mg/day)	=	388
Typical body weight of human	BW (kg)	=	60
Maximum absorption through the skin			
For rinse off products	A (%)	=	2
For leave on products	A (%)	=	2
Dermal absorption per day			
From rinse off products	I x A (mg/day)	=	0.18
From leave on products	I x A (mg/day)	=	7.76
Systemic exposure dose (SED)	I x A/BW (mg/kg/day)		
From rinse off products	0.18 / 60	=	0.003 mg/kg bw/day
From leave on products	6.5 / 60	=	0.129 mg/kg bw/day
Total SED		=	0.132 mg/kg bw/day
No observed adverse effect level	NOAEL (mg/kg/day)	=	50
Systemic NOAEL		=	37.5

(To allow comparison of the oral NOAEL (50 mg/kg bw/d) to dermal systemically available exposure of AEs analogous to polidocanol present in consumer products, a systemic NOAEL of 37.5 mg/kg bw/d was calculated by considering the oral absorption rate of 75% (i.e., 50 mg/kg bw/d x 0.75 = 37.5 mg/kg bw/d)).

Margin of Safety	**NOAEL/SED**	=	**284**

The major route of exposure is via the dermal route. The aggregate exposure to polidocanol due to the potential use of personal care rinse off products containing up to 4% polidocanol, and 3% in general leave on products is calculated to be 0.111 mg/kg bw/day for a 60 kg adult. At this level the Margin of Safety (MOS) is calculated to be 284 for both rinse off and leave on products.

3.3.14. Discussion

The dossier addresses the safety of the use of polidocanol, an alcohol ethoxylate (AE) with an average alkyl chain of 12 to 14 carbon atoms (C_{12-14}) and an ethylene oxide chain of 9 ethylene oxide units (EO_9), in rinse off and in leave on personal care products. Typical concentrations of polidocanol present in personal care products are up to 4% in rinse-off products and up to 3% in leave-on products. For the purpose of this health risk evaluation, it has been assumed that polidocanol is used in rinse off products at up to 4% and in general leave on products at up to 3%. The dermal exposure occurring to the face, hands and the whole body during the cleansing process is the major route of exposure.

A substantial amount of toxicological information and human experience data is available for the AEs similar to polidocanol. The toxicological profile of these AEs indicates that the material has a low order of toxicity, based on a variety of acute, subchronic and chronic toxicity studies. It was neither genotoxic in *in vitro* systems, nor did it cause carcinogenic or reproductive/developmental effects in *in vivo* animal studies. The risk to human health was

characterised by dividing a calculated systemic NOAEL derived from animal toxicity studies by the estimated maximum systemic exposure to calculate the Margin of Safety (MOS). The scenario for dermal exposure to polidocanol from the combined use of rinse off products with maximum polidocanol concentrations of up to 4% in rinse off products and up to 3% in leave on products led to an estimated systemic exposure dose of 0.111 mg/kg bw/d. Dividing the estimated systemic NOAEL of 37.5 mg/kg bw/d by this exposure results in a MOS of 284 for the combined use of rinse-off and leave on products consumed by a 60 kg adult.

Although an assumption of daily aggregate exposure to polidocanol-containing shampoos, hair conditioners, shower gels, hair styling gels, face and body creams is taken to characterize potential health risks associated with polidocanol, the established MoS supports the assessment that the use of polidocanol in rinse off and leave on products poses no human safety concern.

Absorption, distribution, metabolism and excretion (ADME)

Toxicokinetic studies in rats with ^{14}C-labelled AEs $C_{12-15}AE_{3-10}$ demonstrated that these alcohol ethoxylates are readily absorbed in the gastrointestinal tract. It has been estimated that more than 75% of these AEs orally administered are rapidly absorbed and excreted via the urine and faeces. The alkyl chain length appears to have an impact on the metabolism. AEs with longer alkyl chains are excreted at a higher proportion into expired air and less in urine. AEs administered by the dermal route demonstrated incomplete absorption as half of the administered dose was absorbed in 72 hours. The major route of elimination is through urinary excretion.

The metabolism and excretion of radio-labelled AEs $C_{12-13}AE_6$ in humans following oral exposure was comparable to that in rats. The major route of excretion was via the urine as 75% of the radioactivity was found in the urine within the first 24 hours. Excretion via faeces and respired air was 5% and 4%, respectively. Humans exposed to AEs via the dermal route exhibited poor dermal absorption. The maximum systemically available AEs after 144 hours were determined to be 1.82% of the applied dose. The major route of elimination was also via the urine.

Acute toxicity

The AEs analogous to polidocanol was assessed to be of low acute oral and dermal toxicity. The mean acute oral LD_{50} for this class of AEs was > 2000 mg/kg body weight in rats, dogs and monkeys. The dermal application of polidocanol type of AEs to rat skin resulted in LD_{50} > 2000 mg/kg body weight.

Skin toxicity

The skin irritation potential of the AEs similar to polidocanol have been evaluated in rabbits under semi-occluded and occluded exposure conditions at concentrations from 10 to 100% for 4 and/or 24 hours. Observations were made over a period of several days after the exposure and the exposed skin sites were graded for skin irritation according to the Draize scoring scale. Under fully occluded conditions, 4 hour and 24 hour exposure to undiluted AEs resulted in moderate to extreme irritation in rabbit skin. Semi-occluded 24 hour exposure to 10 to 25% of AEs resulted in no irritation. Applied undiluted, semi-occluded 24 hour exposure resulted in mild irritating effects.

The cumulative skin irritation effects of aqueous solutions of polidocanol type of AEs were evaluated under fully occlusive conditions in human 3-Patch application tests. Under the test conditions chosen, only slight irritation to human skin was exhibited. In a single patch test, 10% aqueous solution elicited only a slight skin irritation response.

The skin sensitization potential of AEs analogous to polidocanol was evaluated in two Magnusson-Kligman guinea pig maximization tests. In both studies, the investigated AEs were found to be non-sensitizing at intradermal induction concentrations of 0.01 to 0.2%, topical induction concentrations 15% to 100%, and challenge concentrations up to 60%. In two Buehler tests two AEs of the polidocanol type were not sensitizing when applied undiluted during the induction phase and challenged at concentrations of 50% in aqueous solution.

The absence of skin sensitizing properties of AEs similar to polidocanol were further confirmed in a series of human repeat insult patch tests (i.e., HRIPT) which evaluated formulations containing between 2.5 and 25% AEs. There was no evidence of skin sensitization in humans in any of these studies.

Clinical studies have indicated that polidocanol can act as a contact allergen. Whilst allergy risk was increased in elderly patients with lower leg dermatitis, it was not increased in patients treated for atopic dermatitis with polidocanol containing skin care products. There are only few cases of verified contact sensitization in the general population.

Eye irritation
The application of AEs analogous to polidocanol in neat or varying concentrations of aqueous solutions produces mild to severe irritation in rabbits' eye. Rinsing the eyes shortly after application of the test material decreased the severity of the effects. Generally, concentrations of 0.1 to 1% were non-irritating and concentrations >10% produced moderate irritation. In most cases following exposure, the eyes of the treated animals recovered a few days after exposure.

Systemic toxicity
In a series of 21-day oral feeding studies, AEs similar to polidocanol were examined for repeated dose toxicity. The established NOAELs ranged from 459 to 519 mg/kg bw/day. At higher dose levels the organ mostly affected in these studies was the liver, indicated by increased liver weight and hepatic hypertrophy.

In several 90-day oral subchronic studies, the NOAELs ranged between 50 and 785 mg/kg bw/day. At higher dose levels the investigators observed body weight depressions and in some studies elevated organ-to-body weight ratios in the liver, kidney and heart.

In two chronic toxicity studies, no adverse effects were observed up to dose levels of 50 mg/kg bw/day. At higher dose levels (i.e., 250 and 500 mg/kg bw/day) reduced food consumption, increased organ to body weight ratios and reduced body weight gain was observed.

Genotoxicity and carcinogenicity
AEs that are structurally similar to polidocanol were found not to be mutagenic in the Ames test or clastogenic in the chromosomal aberration test with or without metabolic activation. Also the *in vivo* chromosome aberration studies were negative. The potential for carcinogenicity was further evaluated in two year rat chronic oral feeding studies in which rats were fed with a diet containing AEs at doses up to 1% (500 mg/kg bw/d). There was no evidence of a dose-related increase in tumour incidence at any site and it was therefore concluded that this class of alcohol ethoxylates were not carcinogenic under the test conditions.

Reproductive toxicity
The reproductive toxicity was investigated in two-generation feeding study in rats. The AEs of the polidocanol type investigated did not cause reproduction toxicity. The NOAEL for reproduction toxicity was determined to be greater than 250 mg/kg bw/day. The NOAEL for maternal toxicity was established as 50 mg/kg bw/day. For developmental toxicity a NOAEL greater than 50 mg/kg bw/day was established. At higher exposure levels a reduced pup body weight was observed in the second generation.

Local anaesthetic effects
The possible anaesthetic properties of polidocanol (and other non-ionic surfactants) were investigated in human volunteers, in parallel with proven local anaesthetic agents. In contrast to therapeutically used anaesthetics (lidocaine and prilocaine), the tested surfactants, including polidocanol, had no significant effect on heat and cold sensation. There was no evidence of a local anaesthetic effect in this and in another study which compared the antipruritic effect of several medicinal creams and their basic formulation.

Establishment of a NOAEL for human health risk assessment
For assessing the risk associated with human exposure to polidocanol in context of its use in personal care products, a NOAEL of 50 mg/kg bw/day is used based on a scientifically sound and well conducted 2-year oral feeding study with $C_{12-13}AE_{6.5}$ in rats..
To allow comparison of the oral NOAEL to dermal systemically available exposure of AEs analogous to polidocanol present in consumer products, a conservative systemic NOAEL of 37.5 mg/kg bw/day was estimated by considering a rat oral absorption rate of 75% (i.e., 50 mg/kg bw/d x 0.75 = 37.5 mg/kg bw/day).

4. CONCLUSION

The data included in this dossier demonstrate that polidocanol is of low toxicity and does not pose a risk to the health of the consumer when used up to 3% in leave-on and up to 4% in rinse-off cosmetic products.

Recent scientific evidence does not confirm the assumed local-anaesthetic effect of polidocanol. Thus, its presence in cosmetics and skin care products will not affect cutaneous sensation.

5. MINORITY OPINION

Not applicable

6. REFERENCES

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