



Scientific Committee on Consumer Products

SCCP

OPINION ON

DIETHYLENE GLYCOL MONOETHYL ETHER

(DEGEE)

The SCCP adopted this opinion at its 10<sup>th</sup> plenary of 19 December 2006

### 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 (EMA), 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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[http://ec.europa.eu/health/ph\\_risk/risk\\_en.htm](http://ec.europa.eu/health/ph_risk/risk_en.htm)

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**OPINION ON DIETHYLENE GLYCOL MONOETHYL ETHER (DEGEE)****1. BACKGROUND**

A risk assessment of DEGEE with the chemical name 2-(2-ethoxyethoxy)ethanol or diethylene glycol monoethyl ether was done by a member state (France). The risk assessment is based mainly on open scientific literature and on skin absorptions studies done by Industry. The risk assessment led the member state to put some restrictions on the use of this substance.

According to the notification to the Commission DEGEE is used in cosmetic products in shampoos (rinse-off) in a concentration up to 5% and creams (leave-on) in a concentration up to 2%. It must not be used in products for oral hygiene and the eyes.

The member state concluded that the substance could be considered safe for the consumers, when used in a concentration up to 1.5% cosmetics product except products for oral hygiene.

**2. TERMS OF REFERENCE**

1. *Does the SCCP consider the use of DEGEE in all cosmetics except product for oral hygiene in a concentration up to 1.5% safe for the consumer taken into consideration the scientific data provided?*
2. *If not, does the SCCP foresee any other restrictions to the safe use of DEGEE?*

**3. OPINION****3.1. Chemical and Physical Specifications**

3.1.1. Chemical identity
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3.1.1.1. Primary name and/or INCI name
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UPAC name: 2-(2-Ethoxyethoxy)ethanol  
 INCI name: Ethoxydiglycol

3.1.1.2. Chemical names
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Carbitol, Carbitol solvent, Diethylene glycol monoethyl ether, 3,6-Dioxa-1-octanol, Diethylene glycol ethyl ether, Diethylene glycol monoethyl ether, Diglycol monoethyl ether, Dioxitol, Ethanol, 2,2'-oxybis-, monoethyl ether, Ethyl carbitol, Ethyl diethylene glycol, Ethyl digol,

3.1.1.3. Trade names and abbreviations
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Dowanol 17, Dowanol DE, Ektasolve DE, Solvolisol, Transcutol, Transcutol P, Transcutol HP  
 DEGEE

3.1.1.4. CAS / EINECS/ELINCS number
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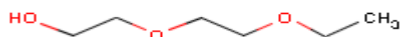
CAS : 111-90-0

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EINECS : 203-919-7

3.1.1.5. Structural formula
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3.1.1.6. Empirical formula
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Formula:  $C_6H_{14}O_3$

3.1.2. Physical form
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Liquid with a mild, pleasant odour. Hydroscopic

3.1.3. Molecular weight
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Molecular weight: 134.2

3.1.4. Purity, composition and substance codes
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Gattefosse states that since May 1998, the manufacturing process of DEGEE was improved, in order to decrease the content in residual impurities:

Transcutol: inferior 99.5%  
 Transcutol P: > 99.7%  
 Transcutol HP: > 99.9%

3.1.5. Impurities / accompanying contaminants
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Impurities: Ethylene glycol. Commercial products may contain an appreciable amount of ethylene glycol (CAS No. 107-21-1).

3.1.6. Solubility
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In water: Miscible

3.1.7. Partition coefficient (Log $P_{ow}$ )
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Log  $P_{ow}$  : - 0.54

3.1.8. Additional physical and chemical specifications
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Appearance : colourless liquid  
 Melting point : - 76 °C  
 Boiling point : 197 – 205 °C  
 Density : 0.988  
 Rel. vap. dens. : /

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Vapour Press. : 0.19 hPa

Conversion:

1 ppm = 5.58 mg/m<sup>3</sup>

1 mg/m<sup>3</sup> = 0.179 ppm

3.1.9.	Stability
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### 3.2. Function and uses

DEGEE may be prepared from ethylene oxide and 2-ethoxyethanol in the presence of SO<sub>2</sub>. It is used in the chemical and paint industries as a solvent for nitro cellulose, resins, and dyes. DEGEE is not used in food or detergent products.

Purified DEGEE (>99%) is used in cosmetics and dermatological preparations and as solvent in some medicine products. DEGEE enhance the percutaneous absorption through the skin and mucosal barriers. It is used in some drugs to enhance absorption.

According to the notification to the Commission DEGEE is used in cosmetic products in shampoos (rinse-off) in a concentration up to 5% and creams (leave-on) in a concentration up to 2%. DEGEE is used in toiletries, skin care, hair care or sun care products which may be applied on the whole body. It must not be used in products for oral hygiene and the eyes.

### 3.3. Toxicological Evaluation

Part of the evaluation is based on a submission "Transcutol Toxicological report summary (Last update: 31/03/2003 from Gattefosse". This submission is unsatisfactory as it contains in most cases only summaries and no details.

3.3.1.	Acute toxicity
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3.3.1.1.	Acute oral toxicity
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The acute toxicity after oral administration of DEGEE has been determined in several experiments. The results are summarized in Table 3.1.

**Table 3.1:** Acute toxicity after oral administration of DEGEE

Species	LD <sub>50</sub> (mg/kg bw)	Reference
Mouse	7410	1
Mouse	6580	2
Rat	7410	1
Rat	5400-5500	3
Rat	6000	4
Rat	6310	5
Rat	8690	6
Rat	5540	2
Rat	>5000	7
Guinea pig	3900	1

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Species	LD <sub>50</sub> (mg/kg bw)	Reference
Rabbit	3600	8

In an isolated case report, an alcoholic male (aged 44) drank approximately 300 ml of a liquid containing 47% DEGEE (about 2000 mg/kg). Severe symptoms of central nervous and respiratory injury (dyspnoea) thirst and acidosis occurred. The urine contained albumin. The subject recovered following symptomatic treatment.

Ref.: 9

**3.3.1.2. Acute dermal toxicity**

The acute toxicity after dermal administration of DEGEE has been determined in several experiments. The results are summarized in Table 3.2.

**Table 3.2:** Acute toxicity after dermal administration of DEGEE

Species	LD <sub>50</sub> (mg/kg bw)	Reference
Mouse	6000	10
Rat	6000	10
Rabbit	8300	10
Rabbit	4200	11
Guinea pig	3200	11

The Hazard Substances Data Bank (HSDB) cites:

.....cosmetic preparations containing more than 5% Carbitol should not be used even for application to small areas of body ...use ... for this purpose may constitute an unexpected hazard, especially if applied to broken skin or in persons with renal disorders.

Ref.: 9

**3.3.1.3. Acute inhalation toxicity**

LC<sub>50</sub> rats = 5240 mg/m<sup>3</sup>

Ref.: 12

*General comment*

DEGEE has low acute toxicity by oral, dermal, and inhalation routes.

**3.3.2. Irritation and corrosivity****3.3.2.1. Skin irritation**

DEGEE (500 mg) was slightly irritant to rabbit skin after 24 hour application.

Ref.: 13

Guideline: /  
 Species/strain: Humans  
 Group size: 10 adult volunteers (females)  
 Test substance: Transcutol  
 Batch: No. 75412  
 Dose level: 0.02 ml, 50 mm<sup>2</sup>  
 Route: Skin  
 Exposure period: 48 hours  
 Observation: /



GCP: In compliance

Transcutol was applied once at the dose level of about 0.020 ml per volunteer, on a surface of about 50 mm<sup>2</sup> of skin on the back of 10 volunteers. Transcutol was kept in contact with the skin under an occlusive patch test for 48 hours. This application was performed in parallel and under same condition with patch test alone as "negative" control. Cutaneous macroscopic examinations were performed about 30 min after removal of the patches. Evaluation of the erythematous and oedematous reactions was made according to a given numerical scale. No reaction of pathological irritation and significant intolerances was noted. It was concluded that the single epicutaneous application of Transcutol under the experimental conditions used was "Well tolerated".

Ref.: 14

### 3.3.2.2. Mucous membrane irritation

DEGEE was slightly irritant to the rabbit eye, Slight pain response, conjunctival redness, thickening of cornea were noted.

Ref.: 15

Guideline: /  
 Species/strain: New Zealand albino rabbits  
 Group size: 3 adult males  
 Test substance: Transcutol  
 Batch: /  
 Dose level: 0.1 ml of a 30% solution  
 Route: Right eye  
 Exposure period: /  
 Observation: 1 h and after 1, 2, 3 days  
 GLP: In compliance

Transcutol was administered in a 30% solution in water for injection into the inferior conjunctival sac of the right eye of 3 male rabbits without rinsing and at the dose level of 0.1 ml per animal. The conjunctiva, iris and cornea were examined 1 h after administration and then on days 1 (24 hrs), 2, and 3. As no more abnormality was noted in the 3 rabbits on day 3, examinations were not continued. Evaluation of the lesions was performed according to the Draize scale. It was concluded that administration of Transcutol at 30% into the eye of the rabbit may be termed "Slightly irritant". The lesions observed 1 h after administration showed a total reversibility on day 1.

Ref.: 16

Guideline: OECD no. 405 (1987)  
 Species/strain: New Zealand albino rabbits  
 Group size: 3 adult males  
 Test substance: Transcutol  
 Batch: /  
 Dose level: 0.1 ml  
 Route: Right eye  
 Exposure period: /  
 Observation: 1 h and after 1, 2, 3 days  
 GLP: In compliance

Transcutol was administered into the inferior conjunctival sac of the right eye of 3 male rabbits without rinsing and at the dose level of 0.1 ml per animal. The conjunctiva, iris and cornea were examined 1 h after administration and then on days 1 (24 hrs), 2, and 3. It was concluded that administration of Transcutol into the eye of the rabbit may be termed "Slightly irritant". No lesions were observed at day 3.

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Ref.: 17

When DEGEE was applied to the eyes of cats, it causes immediate tearing and vigorous rubbing of the eyes, whereas in rabbits the response is less vigorous and the material appears to remain longer in the conjunctival sac. Cats exhibit only slight conjunctival reddening for a day or two, whereas rabbits have been known occasionally to develop conjunctivitis with discharge, iritis, and temporary corneal opacification, with return to normal in a week or two.

Ref.: 18

### *General comment*

DEGEE is moderately irritant to the eye and slightly irritating to the skin.

### 3.3.3. Skin sensitisation

Guideline:	/
Species/strain:	Humans
Group size:	24 adult volunteers (19 – 38 years old)(18 men and 6 women)
Test substance:	Transcutol
Batch:	/
Dose level:	0.02 ml Transcutol
Epicutaneous induction:	Undiluted Transcutol
Challenge:	Undiluted Transcutol
Route:	Occlusive epicutaneous
Exposure period:	10 days
Observation:	15 days
GLP:	In compliance

The Marzulli and Malbach's method was used. 30 volunteers were originally selected. 25 came to the Institute on the day for the first treatment. One of them (a man) abandoned the study on the 12<sup>th</sup> day.

The protocol of the irritation and sensitisation study was allocated into 3 distinct periods.

Induction period. 9 consecutive applications, to the same area, of 0.02 ml, per volunteer, of Transcutol by the occlusive epicutaneous route to the skin of the arm during a 2 week period.

Rest period. 15 days without any application.

Challenge phase. Single application of 0.02 ml Transcutol to the skin of the back.

The cutaneous reaction, control of the primary and cumulative irritations, was evaluated by macroscopic examination of the reactions possibly observed after removal of each patch test corresponding to the induction period. The cutaneous reaction, control of the sensitisation, was evaluated by macroscopic examination of the reactions possibly noted about 24 and 48 h after removal of the patch test corresponding to the challenge application. These examinations were performed for the 1<sup>st</sup>, 8<sup>th</sup> (induction) and 10<sup>th</sup> (challenge) applications, by comparison to the reaction possibly obtained with a patch test alone (without Transcutol).

It was concluded that no pathological irritation or sensitisation reaction significant to a cutaneous intolerance was noted.

Ref.: 19

Human volunteers showed neither irritation nor signs of sensitisation when the material was tested at a 20 percent level in petroleum for a 48 hour closed patch test.

Ref.: 2

### *Comment*

DEGEE has not been demonstrated to cause sensitisation.

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### 3.3.4. Dermal / percutaneous absorption

#### *Shampoo formulations (rinse off)*

Guideline:	OECD 428
Test substance:	5% and 10% DEGEE in a shampoo considered as a "rinse off" reference formulation. ([4- <sup>14</sup> C] DEGEE 53 mCi/mmol, Specific activity at time of application to the skin 81 – 83 µCi/g of formulation)
Batch:	104-272-053 from ADME BIOANALYSES (30 310 Vergeze, France)
Purity:	98.2%
Dose applied:	5 mg/cm <sup>2</sup> of formulation, 279.3 and 529.6 µg/cm <sup>2</sup> DEGEE
Skin preparation:	Human skin
Skin temperature:	37 °C
Exposure period:	30 min
Donor chamber:	Shampoo formulation containing 5% or 10% DEGEE
Receptor fluid:	Saline phosphate buffer (pH 7.4) containing 15 g/l bovine serum albumin
Skin integrity:	TEWL measurement
Recovery:	91%
GLP:	in compliance

Two different DEGEE concentrations 5 and 10% in a shampoo formulation were applied on human skin during a period of 30 minutes. At this time the skin surface was rinsed off. Then the diffusion was monitored until 24 hours. The receptor fluid was completely collected after 30 min, 3, 6, 9, 12 hours and replaced by fresh fluid, the last sampling point was 24 hours. At the end of the 24 hr observation period, the different skin layers were separated (horny layer, epidermis and dermis) and analysed for DEGEE remaining. Results are expressed in µg equivalent of DEGEE (µg/cm<sup>2</sup>) and in % of the applied dose for all the compartment analysed (see table 3.3).

**Table 3.3:** Quantities of DEGEE analysed in the different system compartments for the 2 tested concentrations (5 and 10 %)

	DEGEE 5 %		DEGEE 10 %	
	µg/cm <sup>2</sup>	% of the applied dose	µg/cm <sup>2</sup>	% of the applied dose
Washing (W)	194±4	69±1	389±28	73±5
Receptor fluid (RF)	53.8±22.3	19.37±8	89.7±19.6	16.9±3.0
Total absorbed (E+D+RF)	60.5±29.8	21.6±10.6	92.9±20.8	17.5±3.9
Total recovery (%)	91		91	

Ref.: 20

#### *Hydro-Alcoholic Gel Formulation (leave on)*

Guideline:	OECD 428
Test substance:	15% DEGEE in a "leave on" hydro-alcoholic gel formulation. ([4- <sup>14</sup> C] DEGEE 53 mCi/mmol, Specific activity at time of application to the skin 62 – 65 µCi/g of formulation)
Batch:	104-272-053 from ADME BIOANALYSES (30 310 Vergeze, France)

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Purity:	98.2%
Dose applied:	5 mg/cm <sup>2</sup> of formulation, about 831.4 and 859.1 µg/cm <sup>2</sup>
Skin preparation:	Human skin
Skin temperature:	37 °C
Exposure period:	24 hours
Donor chamber:	Hydro-alcoholic gel formulation containing 15% DEGEE
Receptor fluid:	Saline phosphate buffer (pH 7.4) containing 15 g/l bovine serum albumin
Skin integrity:	TEWL measurement
Recovery:	About 50%
GLP:	in compliance

A 15% DEGEE "leave on" hydro-alcoholic gel formulation was tested in two experiments. The formulation was applied on human skin during a period of 24 hours. The receptor fluid was completely collected after 3, 6, 9, 12 hours and replaced by fresh fluid, the last sampling point was 24 hours. At the end of the 24 hr observation period, the different skin layers were separated (horny layer, epidermis and dermis) and analysed for DEGEE remaining. Results are expressed in µg equivalent of DEGEE (µg/cm<sup>2</sup>) and in % of the applied dose for all the compartment analysed (see table 3.4).

**Table 3.4:** Quantities of DEGEE analysed in the different system compartments in two experiments with 15% DEGEE in a "leave on" hydro-alcoholic gel formulation

	<b>First experiment</b>		<b>Second experiment</b>	
	<b>µg/cm<sup>2</sup></b>	<b>% of the applied dose</b>	<b>µg/cm<sup>2</sup></b>	<b>% of the applied dose</b>
Washing (W)	6.34±1.84	0.77±0.23	7.80±1.64	0.91±0.20
Total absorbed (E+D+S+RF)	425±85	51.0±9.1	385±46	44.9 ±4.8
Total recovery (%)	52±9		46±5	

The percutaneous absorption study was conducted "without occlusion". The "mass balance" of the experiment was low. The low recovery at the end of the 24 hours of diffusion was related to the evaporation of DEGEE from the skin surface. Therefore, the full test was also performed "under occlusion" (by covering the skin with a piece of Parafilm). In the new experiment the total absorbed was 459 µg/cm<sup>2</sup> (51.5%) with a recovery of 92 ± 6%.

Ref.: 21

#### *Emulsified formulations (leave on)*

Guideline:	OECD 428
Test substance:	2%, 5%, and 10% DEGEE in Oil in Water emulsion considered as "leave on" reference formulations. ([4- <sup>14</sup> C] DEGEE 53 mCi/mmol, Specific activity at time of application to the skin 112 – 130 µCi/g of formulation)
Batch:	104-272-053 from ADME BIOANALYSES (30 310 Vergeze, France)
Purity:	98.2%
Dose applied:	5 mg/cm <sup>2</sup> of formulation, 100 – 571 µg/cm <sup>2</sup>
Skin preparation:	Human skin
Skin temperature:	37 °C
Exposure period:	24 hours
Donor chamber:	Oil in Water emulsions containing 2%, 5% or 10% DEGEE

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Receptor fluid:	Saline phosphate buffer (pH 7.4) containing 15 g/l bovine serum albumin
Skin integrity:	TEWL measurement
Recovery:	44 – 52%
GLP:	in compliance

Three different DEGEE concentrations 2, 5 and 10% in an Oil in Water emulsion formulation were applied on human skin during a period of 24 hour. The receptor fluid was completely collected after 3, 6, 9, 12 hours and replaced by fresh fluid, the last sampling point was 24 hours. At the end of the 24 hr observation period, the different skin layers were separated (horny layer, epidermis and dermis) and analysed for DEGEE remaining. Results are expressed in  $\mu\text{g}$  equivalent of DEGEE ( $\mu\text{g}/\text{cm}^2$ ) and in % of the applied dose for all the compartment analysed (see table 3.5 and 3.6).

First experiment

**Table 3.5:** Quantities of DEGEE analysed in the different system compartments for the 3 tested concentrations (2, 5 and 10 %)

	DEGEE 2%		DEGEE 5%		DEGEE 10%	
	$\mu\text{g}/\text{cm}^2$	% of the applied dose	$\mu\text{g}/\text{cm}^2$	% of the applied dose	$\mu\text{g}/\text{cm}^2$	% of the applied dose
Washing (W)	$0.87 \pm 0.3$ 6	$0.87 \pm 0.36$	$1.56 \pm 0.6$ 7	$0.63 \pm 0.29$	$1.82 \pm 0.89$	$0.35 \pm 0.18$
Total absorbed (E+D+RF)	$43.7 \pm 7.0$	$43.2 \pm 4.3$	$140 \pm 28$	$56.1 \pm 12.5$	$267 \pm 43$	$50.4 \pm 7.3$
Total recovery (%)	$44 \pm 4$		$57 \pm 12$		$51 \pm 7$	

Second experiment

**Table 3.6:** Quantities of DEGEE analysed in the different system compartments for the 3 tested concentrations (2, 5 and 10 %)

	DEGEE 2%		DEGEE 5%		DEGEE 10%	
	$\mu\text{g}/\text{cm}^2$	% of the applied dose	$\mu\text{g}/\text{cm}^2$	% of the applied dose	$\mu\text{g}/\text{cm}^2$	% of the applied dose
Washing (W)	$0.98 \pm 1.2$ 5	$0.85 \pm 1.08$	$1.05 \pm 0.3$ 7	$0.36 \pm 0.13$	$1.32 \pm 0.37$	$0.24 \pm 0.11$
Total absorbed (E+D+RF)	$52.7 \pm 7.0$	$45.6 \pm 4.8$	$128 \pm 22$	$44.4 \pm 5.1$	$294 \pm 32$	$51.6 \pm 3.3$
Total recovery (%)	$46 \pm 4$		$45 \pm 5$		$52 \pm 3$	

The percutaneous absorption study was conducted “without occlusion”. The “mass balance” of the experiment was low. The low recovery at the end of the 24 hours of diffusion was related to the evaporation of DEGEE from the skin surface. Therefore, the full test was also performed “under occlusion” (by covering the skin with a piece of Parafilm). In the new experiment the total absorbed was, 2%:  $59.5 \mu\text{g}/\text{cm}^2$  (55.9%) with a recovery of  $85 \pm 14\%$ , 5%:  $167 \mu\text{g}/\text{cm}^2$  (63.8%) with a recovery of  $92 \pm 3\%$ , 10%:  $319 \mu\text{g}/\text{cm}^2$  (56.4%) with a recovery of  $93 \pm 5\%$ .

Ref.: 22

*General comment*

Three well-conducted *in vitro* studies on percutaneous absorption through human skin are available. In a study of a shampoo formulation (rinse off) with a contact time of 30 min,  $21.6 \pm 10.6\%$  was absorbed using a shampoo with 5% DEGEE (total recovery 91%). With 10% DEGEE  $17.5 \pm 3.9\%$  was absorbed (total recovery 91%). In the second study with a hydro-alcoholic formulation (leave on) containing 15% DEGEE  $51 \pm 9.1\%$  was absorbed. The total recovery was however, only  $52 \pm 9\%$ . The low recovery was due to evaporation as the recovery increased to  $92 \pm 6\%$  when performed under occlusion (total absorption 51.5%). The third study involved emulsified formulations (leave on) containing 2, 5, and 10% DEGEE. The total absorption was  $43.2 \pm 4.3$ ,  $56 \pm 12.5$ , and  $50.4 \pm 7.3\%$ , respectively in the first experiment and  $45.6 \pm 4.8$ ,  $44 \pm 5.1$ , and  $51.6 \pm 3.3\%$ , respectively in the second experiment. The total recovery was only between 44 and 53%. When performed under occlusion the recoveries were  $>90\%$ . The absorption with 2% DEGEE was 55.9%.

In the MOS calculation, the results of the 2% emulsified formulation will be used since the maximum concentration in the term of reference was 1.5%. Thus, a dermal absorption of  $45.6 + 2 \times 4.8 = 55.2\%$  will be used in the MOS calculations.

## 3.3.5. Repeated dose toxicity

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

**Oral**Cats

Kidney damage (2 mid doses) and treatment-related mortality (highest dose) were reported in cats treated orally with DEGEE (300, 500, 1000, 4900 mg/kg bw/d) for up to 52 days.

Ref.: 23

Rats

Rats receiving DEGEE in drinking water for 30 days showed reductions in food intake, growth and unspecified micro-pathological changes at all dose levels above approximately 490 mg/kg bw/d.

Ref.: 24

**Dermal**Rabbits

Kidney damage and treatment-related mortality were reported in rabbits following dermal application of DEGEE for 30 days.

Ref.: 10

Guideline:	/
Species/strain:	Young adult New Zealand albino rabbits
Group size:	5 males and 5 females
Test substance:	Transcutol
Batch:	Lot No. 96933
Purity:	/
Dose levels:	0, 100, 300, and 1000 mg/kg bw/day
Route:	Dermal
Exposures:	28 days for a period of 6 h each day
GLP:	In compliance

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New Zealand rabbits, groups of 5 males and 5 females, received 0, 100, 300, and 1000 mg/kg bw/d for 28 days. Transcutol were applied dermally and allowed to remain in contact with the skin for a period of 6 h each day. The test site was covered with one 4 x 6 inch 6-ply gauze pad. The animals were observed for signs of toxicity and mortality each day. Blood was collected from all animals on day 1 and at termination for haematology and blood chemistry evaluation. Complete necropsies were performed on all rabbits.

All treated animals survived and gained weight. Apart from several instances of transient soft faeces during the study, all animals appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. Animals from the exposed groups exhibited barely perceptible erythema and/or oedema and desquamation. The incidence of irritation increased with increasing dose level. Gross necropsy revealed small black masses on the ovaries of 3 females from group 1 (control), 3 (300 mg/kg bw/d), and 4 (1000 mg/kg bw/d). In the affected female from group 3, it was also noted that the left kidney was small in size, tan in color and had small black masses on its surface. Additionally in group 4, the kidneys of 2 males were either mottled tan or irregularly shaped. It was concluded that Transcutol is not toxic when applied dermally and allowed to remain in contact with the skin for 6h/d for 28 days at dose levels up to 1000 mg/kg bw/d.

Ref.: 25

**Inhalation**Rats

SD rats were exposed to 0, 16, 50, and 200 ppm DEGEE (nose-only) for 28 days. There were no signs of systemic intoxication, but there were histopathological changes indicative of mild non-specific irritation in the upper respiratory tract at the mid- and high-exposure levels.

Ref.: 26

Mice, rats, guinea pigs, rabbits, and cats

Daily exposure of mice, rats, guinea pigs, rabbits, and cats to an atmosphere saturated with DEGEE for 12 days was reported not to cause adverse effect.

Ref.: 27

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

**Oral**Rats

Guideline:	/
Species/strain:	Wistar rats (SPF-derived)
Group size:	12 males and 12 females
Test substance:	DEGEE
Batch:	/
Purity:	Contain 0.4% ethylene glycol
Dose levels:	0, 0.25, 1.0, and 5% DEGEE in the diet
Route:	Oral in diet
Exposures:	90 days
GLP:	/

Wistar rats, groups of 12 males and 12 females, received diet containing 0, 0.25, 1.0, and 5.0% DEGEE for 13 weeks. The growth of male and female rats which was significantly retarded at the 5% level was associated with fall in food consumption. No haematological changes were seen at any dietary level. The raised levels of urinary glutamic-oxaloacetic transaminase which occurred in both sexes at the 5% level indicated impaired renal function. This effect was more pronounced in males which also



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showed a high degree of proteinuria. At the 5% level, increases were observed in the relative weights of the kidney in both sexes and of the testes. It was concluded that the NOAEL corresponded to 1% DEGEE in the diet or about 800 mg/kg bw/d.

Ref.: 28

Guideline: /  
 Species/strain: CFE rats (SPF-derived)  
 Group size: 15 males and 15 females  
 Test substance: DEGEE  
 Batch: /  
 Purity: < 0.4% ethylene glycol  
 Dose levels: 0, 0.5, and 5% DEGEE in the diet; Intake, males 0, 570-260, and 5450-2710 mg/kg bw/day, females 0, 470-350, and 5000-3560 mg/kg bw/day  
 Route: Oral in diet  
 Exposures: 90 days  
 GLP: /

CFE rats, groups of 15 males and females, received 0, 0.5, and 5.0% DEGEE in the diet for 13 weeks. At both levels of treatment the rats appeared healthy and there were no deaths. The growth rate was reduced at the highest level of DEGEE. At terminal haematological examination there was a slight anaemia in male rats in the high dose group. The relative kidney weight was significantly increased in the high dose group (14% male, 16% females). Histological examination showed hydropic degeneration of the proximal renal tubules. The males were more affected than the females. It is concluded that NOAEL is about 250 mg/kg bw/d.

Ref.: 29

#### *Comment*

In the documentation received, it is in addition to the two studies above (ref.: 28, 29) referred to a 90 day rat subchronic gavage study (ref.: 30). This study has not been submitted. It is stated:

*"Among the studies submitted to the experts of AFSSAPS, a 90 day subchronic oral (gavage) toxicity study in rats with DEGEE at the unique dose of 180 mg/kg bw/d. Toxicological endpoints measured during the study included clinical observations, body weights, feed consumption, ophthalmology, clinical chemistry (including methemoglobin analysis), haematology, urinalysis, necropsy, organ weights, and histopathology. A toxicokinetic analysis were also performed and the results showed that DEGEE was rapidly absorbed after oral administration to rats and even if the oral bioavailability of DEGEE could not be determined in this study, it was clear that oral administration of DEGEE resulted in a significant systemic exposure to the compound for up to 8 hours after each exposure in male and female rats. No significant toxicity were observed after DEGEE treatment at the single dose level tested. Therefore, the NOAEL for oral DEGEE treatment is 180 mg/kg bw/d. This value is the one used in the calculation of the safety margin, but a new NOAEL may be chosen if new reliable data are submitted to the experts"*

#### Mice

Guideline: /  
 Species/strain: CD-1 mice  
 Group size: 20 males and 20 females  
 Test substance: DEGEE  
 Batch: /



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Purity:	< 0.4% ethylene glycol
Dose levels:	0, 0.2, 0.6, 1.8, and 5.4% DEGEE in the diet; Intake, males 0, 370-270, 1020-800, 3240-2540, and 9930-6980 mg/kg bw/day, females 0, 380-320, 1100-820, 4600-3660, and 12880-9080 mg/kg bw/day
Route:	Oral in diet
Exposures:	90 days
GLP:	/

CD-1 mice, groups of 20 males and 20 females, received 0, 0.2, 0.6, 1.8, and 5.4% DEGEE in the diet for 13 weeks. 10 of the 20 males at the high dose died between week 5 and 12. The growth rate was reduced at the highest level of DEGEE. The relative kidney weight was significantly increased in the high dose group (16% male, 18% females) and next high dose among males (16%). Histological examination showed hydropic degeneration of the proximal renal tubules. It is concluded that NOAEL is about 850-1000 mg/kg bw/d.

Ref.: 29

Pigs

Guideline:	/
Species/strain:	White pigs
Group size:	3 males and 3 females
Test substance:	DEGEE
Batch:	/
Purity:	< 0.4% ethylene glycol
Dose levels:	0, 167, 500, and 1500 mg/kg bw/day DEGEE, top dose decreased to 1000 mg/kg bw/d after 3 weeks
Route:	Oral in diet
Exposures:	90 days
GLP:	/

White pigs, groups of 3 males and 3 females, received 0, 167, 500, and 1500 mg/kg bw/day DEGEE (top dose decreased to 1000 mg/kg bw/d after 3 weeks) in the diet for 13 weeks. 1 male and 2 females at the highest dose were killed between week 2 and 3. These pigs were lethargic for the terminal 4-5 days and became comatose with a slow laboured respiration during the last 24 h. The body weights were not reduced during the treatment and increased from about 10 kg to 35 kg during the 13-week treatment. There was a slight anaemia in male pigs at the highest dose. The killed pigs had a more severe anaemia associated with a reduced haematocrit and erythrocyte count. The absolute and relative kidney weight was increased in the high dose group. Histological examination showed hydropic degeneration of the proximal renal tubules at the highest level of treatment and at 500 mg/kg bw/d. It is concluded that NOAEL was 167 mg/kg bw/d.

Ref.: 29

**Dermal**Rabbits

Rabbits receiving dermal treatments (not further specified) of DEGEE for 90 days showed no effects on growth, mortality, haematology, clinical chemistry or gross pathology at dose level up to 300 mg/kg bw/d. A treatment related histopathological effect was seen in the kidneys of animals at 1000 and 3000 mg/kg bw/d.

Ref.: 31

**Inhalation**

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### Rats

Continuous DEGEE inhalation exposure of rats at 0.27 and 4.5 ppm for 4 months followed by a recovery period resulted in changes in blood cell (anaemia) and chemistry profiles as well as CNS effects.

Ref.: 32

3.3.5.3. Chronic (> 12 months) toxicity
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### **Oral**

#### Rats

In a 2-year dietary study with rats, employing limited pathological examination, rats were exposed for 2 years on a diet containing 2.16% of purified DEGEE. This is probably equivalent to slightly more than 1.0 g/kg/day. The only adverse effects noted were a few oxalate crystals in a kidney of one animal, slight liver damage, and some interstitial oedema in the testes. Since the quality of the material tested was not established, the possibility of the crystals being caused by the presence of small amounts of ethylene glycol in the test sample cannot be overlooked.

Ref.: 33

Albino rats receiving two grades of DEGEE through three generations (Fo, F1 and F2) during a 2-year period. One grade contained 0.2% ethylene glycol and the other 29.5% ethylene glycol. The drinking water levels were 0, 0.01, 0.04, 0.2, and 1% (10, 40, 200 and 950 mg/kg bw/d). F1 and F2 generations received the same dosage levels as the parents, and all survivors were killed 718 days from the start of the test. The sample that contained 29.5% ethylene glycol was considerably more toxic than the purer grade. The "toxic" group constituted 16 rats showing severe injury, notably kidney damage or bladder concretions; the animals comprised 39% of animals receiving 950 mg/kg bw and 11% of animals receiving 200 mg/kg bw DEGEE with 29.5% ethylene glycol and 7% of animal receiving 950 mg/kg bw DEGEE with 0.2% ethylene glycol. It was concluded that the maximum safe dose of the impure material was 10 mg/kg bw/d whereas it was about 200 mg/kg bw/d for the purer sample.

Ref.: 34

#### Rats and mice

In an incomplete study DEGEE caused no apparent adverse effects when presented at 1% concentration in the drinking water to rats or mice for up to 23 months.

Ref.: 1

#### Ferrets

Ferrets showed no adverse treatment related effects following dietary feeding with DEGEE at concentrations ranging from 490 to 2960 mg mg/kg bw/d for 9 months.

Ref.: 37

#### *General comment*

Three oral subchronic oral studies in rats are discussed. DEGEE was added to the diet in two of the studies. In one study with Wistar rats a NOAEL of 800 mg/kg bw/d was reported and in a study with CFE rats a NOAEL of 250 mg/kg bw/d (0.5% DEGEE in the diet) was concluded. In the third study the rats received DEGEE by gavage. No significant effects were observed at the only dose tested. The French authorities used this study for their NOAEL of 180 mg/kg bw/d.

In an oral mice study with DEGEE added to the diet a NOAEL of 850 – 1000 mg/kg bw/d was concluded. In a similar small study with white pigs and the following doses; 0, 167, 500, and 1500 mg/kg bw/d, NOAEL of 167 mg/kg bw/d was concluded. Histological examination showed hydropic degeneration of the proximal renal tubules at the highest level of treatment and at 500 mg/kg bw/d.

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From a two year chronic drinking water study with albino rats, a NOAEL of 200 mg/kg bw/d was obtained with a preparation containing 0.2% ethylene glycol. This value will be used in calculation of MOS.

### 3.3.6. Mutagenicity / Genotoxicity

#### 3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

DEGEE displayed a weak mutagenic activity at high concentrations in some tested *Salmonella typhimurium* strains (TA1535, TA1537, TA1538) and in *Saccharomyces cerevisiae* (D7)

Ref.: 1

Guideline:	/
Species/strains:	<i>Salmonella typhimurium</i> TA98, TA100, TA102, TA1535, and TA1537
Test substance:	Transcutol P
Batch:	/
Purity:	/
Replicates:	Two independent experiments in triplicate
Concentrations:	Experiment 1: 0 (control), 52, 164, 512, 1600, and 5000 µg/plate Experiment 2: 0 (control), 492, 878, 1568, 2800, and 5000 µg/plate
Controls:	Negative and positive (substances not given)
Preincubation test:	/
Test conditions:	Standard plate test and preincubation test both with and without metabolic activation (Type not stated)
GLP:	In compliance

Transcutol P was tested on 5 strains of *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) in the presence and absence of metabolic activation. Concentrations of Transcutol P used are stated above. No signs of cytotoxicity (such as a reduction of the bacterial lawn and/or a decrease in number of revertants with evidence of a dose relationship) and no precipitate were noted. It was concluded that under the experimental conditions that Transcutol P did not induce any mutagenic effect in the test either with or without metabolic activation.

Ref.: 37

#### 3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

DEGEE did not induce micronuclei in CD-1 mouse bone marrow following 2 daily i.p. injections at 1980 mg/kg bw.

Ref.: 1

### Unscheduled DNA synthesis (UDS) test in primary rat hepatocytes *in vivo*

Guideline:	/
Species/strain:	Wistar rats
Group size:	5 males
Test substance:	Transcutol
Concentrations:	800 and 2000 mg/kg bw
GLP:	In compliance

Groups of 5 male rats were treated once with Transcutol at 800 and 2000 mg/kg bw by gavage at a dose volume of 10 ml/kg bw. 75 mg/kg bw of 2-acetamidofluorene (2-AAF) was

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used as positive control animals for the 12 –14 h experiment and 10 mg/kg bw of dimethylnitrosamine (DMN) was used as positive control for the 2 – 4 h experiment.

Approximately 12 – 14 h (experiment 1) and 2 – 4 h (experiment 2) after dosing, the animals were killed and their livers perfused with collagenase to provide a primary culture of hepatocytes. Cultures were made from 3 animals in each dose group and were treated with [<sup>3</sup>H] thymidine. Six slides from each animal were prepared with fixed hepatocytes and of these 3 were dipped in photographic emulsion to prepare autoradiograms. Slides were examined microscopically and net grain count (NNG) was determined for each of two of the three slides, each animal and dose group. Negative control gave a group mean NNG value of less than zero with only 0.7 – 1% cells in repair. Group mean NNG values were increased by 2-AAF and DMN treatment to more than 5 and more than 50% cells found to be in repair. Treatment with 800 and 2000 mg/kg Transcutol did not produce NNG value greater than –1.7 nor were more than 0.7% cells found in repair at either dose. It was concluded that Transcutol did not induce UDS detectable under the experimental conditions employed.

Ref.: 38

*General comment*

In one purely reported study DEGEE displayed a weak mutagenic activity at high concentrations in some tested *Salmonella typhimurium* strains (TA1535, TA1537, TA1538) and in *Saccharomyces cerevisiae* (D7) while no mutagenic activity were reported in another *Salmonella* test. DEGEE did not induce unscheduled DNA synthesis (UDS) test in primary rat hepatocytes *in vivo* after exposure of rats up to 2000 mg/kg bw by gavage. In one poorly reported study DEGEE did not induce micronuclei in CD-1 mouse bone marrow following 2 daily i.p. injections at 1980 mg/kg bw.

3.3.7.	Carcinogenicity
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No adequate data available

3.3.8.	Reproductive toxicity
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**Oral route**Mice

Guideline:	/
Species/strain:	Swiss CD-1 mice
Group size:	50 pregnant mice
Test substance:	DEGEE
Batch:	/
Purity:	>99%
Dose levels:	5500 mg/kg bw/d
Route:	Oral, gavage
Exposures:	Pregnant mice, days 7 through 14 of gestation
GLP:	In compliance

Fifty mated CD1 mice were orally administered DEGEE (>99% purity) by gavage at 5500 mg/kg/day (calculated LD<sub>10</sub> based on a non-pregnant mouse pilot study) in corn oil from GD7-14 (GD1=vaginal sperm plug), then allowed to litter and to rear pups to PND3. 14% of the dams died, maternal weight gain was reduced and, of 33 surviving pregnant females, there were 32 viable litters (97%) compared with 100% control litter viability. No external malformations were seen, pup survival to PND was unaffected and no other indication of specific developmental toxicity was found.

Ref.: 39, 40

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Guideline: /  
 Species/strain: CD-1 outbred Swiss albino mice  
 Group size: 20 males and 20 females; control group 40 males and 40 females  
 Test substance: DEGEE  
 Batch: /  
 Purity: >99%  
 Dose levels: 0, 0.25, 1.25, and 2.5% (440, 2200, and 4400 mg/kg bw/d)  
 Route: Oral, in drinking water  
 Exposures: See below  
 GLP: /

*Continuous breeding*

During the first 7 days of treatment (premating exposure) the sexes were housed separately. Subsequently, females and males from the same dose group were paired and cohabited for 98 days while being continuously exposed to DEGEE. The pairs were then separated and exposed for further 3 weeks. The animals received DEGEE in drinking water at concentrations of 0, 0.25, 1.25, and 2.5% (440, 2200, and 4400 mg/kg bw/d). During the 119 day period, different reproduction parameters were recorded. There was a small significant decrease in the mean body weights of the males during weeks 1 and 5 in the high dose group. DEGEE had only minimal effects on fertility or reproductive performance.

*Offspring assessment.* The F<sub>1</sub> generation from the final litters was reared and continuously treated with 0 or 2.5% DEGEE and at 74±10 days of age paired with nonsiblings from the same dose group. A significant decrease (34%) in motile sperm from de cauda epididymis in males exposed to 2.5% DEGEE. In addition the relative liver weights were increased (16% males and 10% females).

Ref.: 41, 42

Rats

Rats, groups of 24 males and 24 females, received 0, 300, 1000, and 2000 mg/kg bw/d with Transcutol HP with gavage daily during premating (63 days for males, 14 days for females) and during mating. Dosing continued until gestation day 7 for females and until the day prior to necropsy for males (20 days after mating). All dose levels of Transcutol HP up to 2000 mg/kg bw/d were well tolerated in rat, although minor effects on clinical condition and body weight was observed at the higher dose levels (mainly in males). There were no effects of DEGEE on gonadal function, fertility and reproductive performance in any group. It was concluded that NOAEL for fertility was 2000 mg/kg bw/d and that NOAEL for general toxicity was 1000 mg/kg bw/d.

Ref.: 43

Pregnant female rats received 0, 300, 1000, and 2000 mg/kg bw/d with Transcutol by gavage from day 6 to day 17 of gestation. The animals were killed at day 20 for maternal, foetal soft tissue and skeletal evaluations. The highest dose level of 2000 mg/kg bw/d of Transcutol HP resulted in slight maternal toxicity characterised by reduction in body weight gain and food consumption. There was no evidence of maternal toxicity in lower dose groups. Evidence of embryo-foetal toxicity was restricted to minor skeletal findings which principally included a dose-related increase in the incidence of reduced ossification of cranial bones in the 1000 and 2000 mg/kg bw/d groups. These minor skeleton findings were considered not to be indicative of a teratogenic potential of Transcutol HP, but suggested a selective effect on the developing foetuses in view of the limited maternal toxicity in the high dose group and the absence of an effect on foetal weight. The dose of 1000 mg/kg bw/d was considered a NOAEL for maternal toxicity. The dose of 300 mg/kg bw/d was considered NOAEL for embryo-foetal toxicity. It was concluded that there was no indication of teratogenicity at any dose level used in the study.

Ref.: 44

## Dermal route

### Rats

Guideline: /  
 Species/strain: Sprague-Dawley rats  
 Group size: 13 rats, control 17 rats  
 Test substance: DEGEE  
 Batch: Lot 792796  
 Purity: /  
 Dose levels: 0.35 ml x 4 per day from GD 7 – 16  
 Route: Skin  
 Exposures: 10 days  
 GLP: /

DEGEE was applied to the skin (unoccluded) of 13 pregnant SD rats to investigate its potential for developmental toxicity. Four doses each 2.5 hours apart of 350 mg DEGEE (total daily dose of 1400 mg, 5600 mg/kg bw/day) were applied daily to shaved interscapular skin of rats on GD 7 – 16 (GD0 = sperm positive). Extragestational weight gain in the DEGEE rats was significantly less than in the water controls. Thus, DEGEE caused a slight maternal toxicity. No embryotoxic, foetotoxic, or teratogenic effects were, however, detected with DEGEE treatment at the concentration of approximately 5600 mg/kg bw/day.

Ref.: 45

### *Comment*

No clear conclusion can be drawn from the findings of this study since DEGEE was applied to the skin without occlusion, which would potentially enable evaporative loss from the site of application.

## Inhalation

### Rats

Sprague-Dawley rats, a group of 15 pregnant female rats were exposed to 0, 100 ppm DEGEE for 7 h/d from day 7 to day 15 of gestation. The animals were killed for necropsy at day 20. No selective developmental toxicity was seen under the treatment conditions. It was concluded that DEGEE was not a developmental toxicant.

Ref.: 46

### *General comment*

DEGEE has low toxicity on reproductive performance and development. Evidence of embryo-foetal toxicity was restricted to minor skeletal findings which principally included an increase in the incidence of reduced ossification of cranial bones. These minor skeleton findings were not considered to be indicative of a teratogenic potential, but suggested a selective effect on the developing foetuses. In a rat study the dose of 1000 mg/kg bw/d was considered a NOAEL for maternal toxicity. The dose of 300 mg/kg bw/d was considered to be the NOAEL for embryo-foetal toxicity.

3.3.9. Toxicokinetics
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An anecdotal report of rabbits treated orally or by s.c. injection indicated degradation of DEGEE and elimination in the urine as glucuronic conjugates.

Ref.: 47

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DEGEE given orally to an adult human at a dose of about 20 mg/kg bw resulted in formation of 2-(2-ethoxyethoxy)acetic acid as a major (68% of the dose) metabolite in the urine.

Ref.: 48

3.3.10. Photo-induced toxicity
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3.3.10.1. Phototoxicity / photoirritation and photosensitisation
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3.3.10.2. Phototoxicity / photomutagenicity / photoclastogenicity
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3.3.11. Human data
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No data submitted

3.3.12. Special investigations
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No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)
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### CALCULATION OF THE MARGIN OF SAFETY

#### Diethylene glycol monoethyl ether (DEGEE)

The safety calculation is only considering dermal exposure.

*Maximum dermal absorption of test substance reported was 55.2%*

*NOAEL based on kidney damage or bladder concretions in albino rats was 200 mg/kg bw/d*

*Exposure 17.79 (total) – 3.52 (oral product) = 14.27 g/d, 1.5% DEGEE = 214 mg/d.*

Maximum absorption through the skin	$214 \times 55.2/100$	=	118 mg/d
Typical body weight of human		=	60 kg
Systemic exposure dose (SED)	$118/60$	=	1.97 mg/kg
No observed adverse effect level (mg/kg) NOAEL (albino rats 2 year oral study)		=	200 mg/kg

<b>Margin of Safety</b>	<b>NOAEL / SED</b>	<b>=</b>	<b>102</b>
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A MOS of 102 is considered to give sufficient protection in relation to the use of DEGEE as a solvent in cosmetics (with exception of oral products).

3.3.14. Discussion
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The safety has only been considered for dermal exposure.

The influence of possible evaporation in the various experiments has not been considered.

*Physico-chemical specification*



The stability of diethylene glycol monoethyl ether (DEGEE) is not reported. The physico-chemical characterisation and purity of the substance is not reported in several studies. Commercial products of DEGEE may contain an appreciable amount of ethylene glycol. Part of the evaluation is based on a submission "Transcutol Toxicological report summary (Last update: 31/03/2003 from Gattefosse". This submission is unsatisfactory as it contains in most cases only summaries and no details.

#### *General toxicity*

The toxicity data on DEGEE indicates that this glycol ether produces little repro- or haemato-toxicity, which are of concern with several other glycol ethers. However, some systemic toxicity has been reported. DEGEE may contain ethylene glycol as impurity. It is recommended that the level of ethylene glycol in DEGEE preparations used in cosmetics should be <0.2%.

DEGEE has low acute toxicity by oral, dermal, and inhalation routes.

Three oral subchronic oral studies in rats are discussed. DEGEE was added to the diet in two of the studies. In one study with Wistar rats a NOAEL of 800 mg/kg bw/d was reported and in a study with CFE rats a NOAEL of 250 mg/kg bw/d (0.5% DEGEE in the diet) was concluded. In the third study the rats received DEGEE by gavage. No significant effects were observed at the only dose tested. The French authorities used this study for their NOAEL of 180 mg/kg bw/d. A NOAEL of 200 mg/kg bw/d was calculated from a two year drinking water study with rats.

In a oral mice study with DEGEE added to the diet a NOAEL of 850 – 1000 mg/kg bw/d was concluded. In a similar study with white pigs and the following doses; 0, 167, 500, and 1500 mg/kg bw/d, NOAEL of 167 mg/kg bw/d was concluded. Histological examination showed hydropic degeneration of the proximal renal tubules at the highest level of treatment and at 500 mg/kg bw/d.

A NOAEL can be calculated from several oral studies. In studies of rats the NOAEL varied from 180 to 800 mg/kg bw/day, in mice it was about 850 – 1000 mg/kg bw/d, while in pigs a NOAEL of 167 mg/kg bw/d was reported after gavage. In the MOS calculation a NOAEL of 200 mg/kg bw/d based on kidney damage or bladder concretions in albino rats is used.

DEGEE given orally to an adult human at a dose of about 20 mg/kg bw resulted in formation of 2-(2-ethoxyethoxy)acetic acid as a major (68% of the dose) metabolite in the urine.

#### *Irritation /sensitisation*

DEGEE is moderately irritant to the eye and slightly irritating to the skin. It has not been demonstrated to cause sensitisation.

#### *Reproductive toxicity*

DEGEE has low toxicity on reproductive performance and development. Evidence of embryo-foetal toxicity was restricted to minor skeletal findings which principally included an increase in the incidence of reduced ossification of cranial bones. These minor skeleton findings were not considered to be indicative of a teratogenic potential, but suggested a selective effect on the developing foetuses. In a rat study the dose of 1000 mg/kg bw/d was considered a NOAEL for maternal toxicity. The dose of 300 mg/kg bw/d was considered NOAEL for embryo-foetal toxicity.



**OPINION ON DIETHYLENE GLYCOL MONOETHYL ETHER (DEGEE)***Dermal absorption*

Three well-conducted *in vitro* studies on percutaneous absorption through human skin are available. In a study of a shampoo formulation (rinse off) with a contact time of 30 min,  $21.6 \pm 10.6\%$  was absorbed using a shampoo with 5% DEGEE (total recovery 91%). With 10% DEGEE  $17.5 \pm 3.9\%$  was absorbed (total recovery 91%). In the second study with a hydro-alcoholic formulation (leave on) containing 15% DEGEE  $51 \pm 9.1\%$  was absorbed. The total recovery was however, only  $52 \pm 9\%$ . The low recovery was due to evaporation as the recovery increased to  $92 \pm 6\%$  when performed under occlusion (total absorption 51.5%). The third study involved emulsified formulations (leave on) containing 2, 5, and 10% DEGEE. The total absorption was  $43.2 \pm 4.3$ ,  $56 \pm 12.5$ , and  $50.4 \pm 7.3\%$ , respectively in the first experiment and  $45.6 \pm 4.8$ ,  $44 \pm 5.1$ , and  $51.6 \pm 3.3\%$ , respectively in the second experiment. The total recovery was only between 44 and 53%. When performed under occlusion the recoveries were  $>90\%$ . The absorption with 2% DEGEE was 55.9%.

In the MOS calculation the results of the 2% emulsified formulation will be used since the maximum concentration in the term of reference was 1.5%. Thus, a dermal absorption of  $45.6 + 2 \times 4.8 = 55.2\%$  will be used in the MOS calculations.

*Mutagenicity*

In one poorly reported study DEGEE displayed a weak mutagenic activity at high concentrations in some tested *Salmonella typhimurium* strains (TA1535, TA1537, TA1538) and in *Saccharomyces cerevisiae* (D7) while no mutagenic activity were reported in another *Salmonella* test. DEGEE did not induce unscheduled DNA synthesis (UDS-test) in primary rat hepatocytes *in vivo* after exposure of rats up to 2000 mg/kg bw by gavage. In one poorly reported study DEGEE did not induce micronuclei in CD-1 mouse bone marrow following 2 daily i.p. injections at 1980 mg/kg bw. It is noted that no *in vitro* mammalian genotoxicity studies are available. However, two negative *in vivo* studies are available and based on the structure of the substance it is not expected that DEGEE will have relevant mutagenic potential *in vivo*. On this basis SCCP will not ask for an *in vitro* mammalian genotoxicity study.

*Carcinogenicity*

No adequate carcinogenicity study is available.

**4. CONCLUSION**

Based on the information provided, the SCCP is of the opinion that the use of diethylene glycol monoethyl ether (DEGEE) in all cosmetic products, except products for oral hygiene and eye products at a concentrations up to 1.5% does not pose a risk to the health of the consumer, provided that the level of ethylene glycol in DEGEE used is  $< 0.2\%$ .

The opinion relates to the dermal application. It does not include any other cosmetic exposure, such as exposure from possible aerosol/spray products.

**5. MINORITY OPINION**

Not applicable

**6. REFERENCES**

**OPINION ON DIETHYLENE GLYCOL MONOETHYL ETHER (DEGEE)**

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