EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

OPINION ON

DIETHYLENE GLYCOL MONOBUTYL ETHER

(DEGBE)

Opinion adopted by the SCCP during the 10th plenary of 19 December 2006

ACKNOWLEDGEMENTS

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1. BACKGROUND

A risk assessment of DEGBE with the chemical name 2-(2-butoxyethoxy)ethanol or diethylene glycol monobutyl 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 this substance.

According to the notification to the Commission DEGBE is used in cosmetic products only as a solvent in hair dyes.

Based on a NOAEL 2000 mg/kg and 100% absorption as no study was available the member state concluded that the substance could be considered safe for the consumers, when used in a concentration up to 9% in hair dyes.

2. TERMS OF REFERENCE

1. *Does the SCCP consider the use of DEGBE as solvent in hair dyes in a concentration up to 9% 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 DEGBE?*

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

UPAC name: 2-(2-Butoxyethoxy)ethanol
INCI name: Butoxydiglycol

3.1.1.2. Chemical names

Butoxyethoxyethanol, butyl carbitol, butyl diglycol, butyl diglycol ether, butyl digol, butyl dioxitol, butoxydiethylene glycol, butoxydiglycol, diethylene glycol butyl ether, diglycol monobutyl ether

3.1.1.3. Trade names and abbreviations

Caswell No 121 B, Caswell No 125H, Dowanol DB, Ektasolve DB, Poly-solve DB

BUCB, DEGBE

3.1.1.4. CAS / EINECS/ELINCS number

CAS: 112-34-5
EINECS: 203-961-6

3.1.1.5. Structural formula

3.1.1.6. Empirical formula

Formula: $C_8H_{18}O_3$

3.1.2. Physical form

Liquid with a faint butyl odour

3.1.3. Molecular weight

Molecular weight: 162.23

3.1.4. Purity, composition and substance codes

Purity: >99%

3.1.5. Impurities / accompanying contaminants

Impurities:	2-butoxyethanol (CAS No 111-76-2)	< 0.5% w/w
	2-(2-propenyloxy)ethanol (CAS No 111-46-6)	< 0.25% w/w
	2-(2-methylpropoxy)ethanol (CAS No 4439-24-1)	< 0.2% w/w
Additives:	Butylated hydroxytoluene (BHT) (CAS No 128-37-0)	0.004-0.006% w/w

3.1.6. Solubility

In water: miscible

Very soluble in ether, alcohol and acetone, soluble in benzene

3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow}: 0.56

3.1.8. Additional physical and chemical specifications

Appearance	:	Colourless liquid
Melting point	:	- 68 °C
Boiling point	:	228 – 234 °C (1013 hPa)
Density	:	0.948 – 0.96 (20 °C)
Rel. vap. dens.	:	/

Vapour Press. : 0.027 hPa (20 °C)

Conversion
1 ppm = 6.75 mg/m^3
1 mg/m^3 = 0.148 ppm

3.1.9.	Stability

/

3.2. Function and uses

DEGBE belongs to the group of glycol ethers, which are mainly used as solvents. During 1991 – 1993, the production of DEGBE in the European Union ranged from 20,000 to 80,000 tonnes. DEGBE is produced by the reaction of ethylene oxide and n-butanol with an alkalic catalyst.

DEGBE has a wide range of uses as a solvent in paints, dyes, inks, detergents and cleaners. The major function is to dissolve various components of mixtures in both aqueous and non-aqueous systems. Nearly 60% of DEGBE in Europe is used in cleaning agents and about 35% in paints and surface coatings.

DEGBE is used in cosmetic products in France at a maximum concentration of 9%. DEGBE is not used in food and medicine products. According to the notification to the Commission, DEGBE is used in cosmetic products only as a solvent in hair dyes.

3.3. Toxicological Evaluation

Part of the toxicological evaluation is based on the EU risk assessment – 2-(2-butoxyethoxy)ethanol.

Ref.: 1

3.3.1.	Acute toxicity

3.3.1.1.	Acute oral toxicity

The acute toxicity after oral administration of DEGBE has been determined in several experiments. The results are summarized in Table 3.1.

Table 3.1. *Acute toxicity after oral administration of DEGBE*

Species	**LD_{50} (mg/kg bw)**	**Reference**
Mouse	2400	2
Mouse (fed)	5526	3
Mouse (fasted)	2406	3
Rat	5660	2
Rat	6560	4
Rat (fed)	9623	3
Rat (fasted)	7292	3
Guinea pig	2000	2
Rabbit	2200	5

Rabbit	2700	2

Human exposure – 2 ml/kg has produced cyanosis, tachypnea, and slight uremia.

Signs of toxicity before death in orally treated mice and rats included inactivity, laboured breathing, rapid respiration, anorexia, weakness, tremors and prostration.

Ref.: 3

3.3.1.2. Acute dermal toxicity

Rabbit: LD_{50} = 2764 mg/kg.
Anorexia, enlargement of the kidneys, discoloration of the renal pelvis, and oedematous and haemorrhagic in the thymus were observed in the treated rabbits.

Ref.: 6

General comment
DEGBE has low acute toxicity by oral and dermal routes.

3.3.1.3. Acute inhalation toxicity

No rats died when exposed for 7 hr to the maximum attainable vapour concentration of DEGBE, estimated to be 18 ppm (120 mg/m^3).

Ref.: 7

Comment
The available data do not allow a definite conclusion on acute toxicity of DEGBE by inhalation.

3.3.2. Irritation and corrosivity

3.3.2.1. Skin irritation

DEGBE was slightly irritant to rabbit skin upon prolonged or repeated exposure.

Ref.: 8

3.3.2.2. Mucous membrane irritation

DEGBE (0.1ml) was moderately irritant to the rabbit eye. Effects were most severe within the first 24 hrs, the eye returned to normal within 14 days.

Ref.: 9

General comment
DEGBE is moderately irritant to the eye and slightly irritating to the skin.

3.3.3. Skin sensitisation

DEGBE was a non-sensitiser in guinea pig maximisation test (25% injection induction. 100% application induction and application challenge).

Ref.: 10

A single case of allergic contact dermatitis following occupational exposure over a 20-year period.

Ref.: 11

Comment

No conclusion on sensitisation can be drawn due to lack of information in relation to the available experiment.

3.3.4. Dermal / percutaneous absorption

In vivo

Guideline:	/
Species/strain:	Sprague-Dawley rats
Groups:	4 male (244-326 g bw) and 4 female (194-236 g bw)
Test substance:	DEGBE, [U-^{14}C-ethylene]DEGBE
Batch:	/
Purity:	> 99%
Dose applied:	200 and 2000 mg/kg bw
Skin preparation:	7.5 cm^2 shaved skin
Exposure period:	24 hours under occlusion
Recovery:	81 – 89%
GLP:	/

Absorption, metabolism, and excretion were studied in rats (7 to 9 weeks old at the time of dosing) dermally exposed to ^{14}C-DEGBE at dose levels of 200 (undiluted and 10% aqueous solution) and 2000 mg/kg bw (undiluted) for 24 hours under occlusion at a surface area of 7.5 cm^2. After 24 hours ^{14}C was determined in the patch and washing liquid (water). Urine, cage wash, and faeces were collected during 7 days in 24 hours samples for ^{14}C determination.
At the end of the study ^{14}C was determined in the carcasses and the dermal exposure sites. Total recovery ranged from 81 to 89%. DEGBE was incompletely absorbed.
In rats at low dose group 33 and 30% of the applied dose was absorbed in males and 43 and 54% in females for diluted and undiluted solutions, respectively. In the males of the high dose group 3.4% of the applied dose was absorbed and in the females 19%. Urinary excretion accounts for the majority of the recovered ^{14}C in both dose groups. In the low dose group urinary excretion was 31 and 27% of the applied dose in males, and 42 and 51% in females for diluted and undiluted solutions, respectively. In the high dose group 3.3% of the applied dose was excreted in urine in males, and 18% in females. The majority was excreted within 24 hours after the start of the study. The major urinary metabolite was 2-(2-butoxyethoxy)acetic acid (61 – 80% of total urinary radioactivity). The glucuronic acid of DEGBE was present at levels ranging from 5.2 to 8.2% of the urinary ^{14}C.

Ref.: 12

The *in vitro* absorption of DEGBE through human skin was evaluated. The test substance as a neat liquid was left in contact with the skin for approximately 8 hours. An apparent lag phase of 2 - 2.5 hours was observed followed by a steady rate of penetration. The mean steady rate of absorption for DEGBE was 0.033 mg/cm^2/hour. No significant irreversible alterations to the barrier properties of the epidermal were observed.

Ref.: 13

In vitro percutaneous absorption of DEGBE was evaluated using Franz-type glass diffusion cells and 4 full thickness skin samples obtained from each of 2 male Sprague-Dawley rats. The mean permeability constant for DEGBE was 0.53 x 10-3 cm/h and the mean absorption rate was 0.51 mg/cm^2/h.
The authors extrapolated the data to human exposure and concluded that immersion of both hands (740 cm^2 surface area) of a 70 kg human in DEGBE for an hour would result in an absorption of 5.4 mg DEGBE/kg.

Ref.: 14

In an absorption study, the permeability of human abdominal skin to DEGBE was measured *in vitro* using Franz-type glass diffusion cells. Epidermal layers from human skin were exposed for 8 hours to a solution containing radio-labelled test compound in the donor

chamber and the appearance of radioactivity was measured in the receptor chamber. Damage to skin was calculated by comparing the water absorption rates of skin before and after exposure to the test compound. The rate of absorption of the test compound across human skin was 0.03 mg/cm^2/hr. Exposure to the test chemical did not alter the permeability of skin to water.

Ref.: 15

Comment
None of the studies comply with accepted guideline and GLP. In the EU Risk Assessment Report (ref.: 1) it was concluded: *"From the dermal studies it is concluded that complete dermal absorption cannot be excluded. For risk characterisation 100% dermal absorption should be assumed (worst-case estimate)."* In Submission, the French Authorities states: *"Because no reliable data are available on skin absorption, it is assumed that the entire amount applied to the skin is absorbed."* However, based on the experiments reported above and well-conducted dermal absorption study with EGBE and DEGEE (see Opinion 1045/06 and 1044/06 by SCCP) it is unlikely that the dermal absorption is larger than 50%.

3.3.5. Repeated dose toxicity

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

Oral, rat
Sherman rats, groups of 5 males and 5 females received 0, 51, 650, and 1830 mg/kg bw/day of DEGBE by gavage for 30 days. No effects were observed at 51 mg/kg bw/day. The food intake was reduced and slight (unspecified micro-pathological) changes in liver, kidney, spleen or testis were observed at the higher doses. NOAEL was 51 mg/kg bw/day.

Ref.: 16

CD rats, groups of 10 males received 0, 891, 1782, and 3564 mg/kg bw/day of DEGBE by gavage for 7 d/wk for 6 wk. Hyperkeratosis in stomach (possibly fore-stomach) was observed at all doses. Increase in relative liver weight (statistically non-significant) was observed at low dose. At mid and high doses; decrease in red blood cell count, Hb, MCH, increased spleen weights (absolute and relative), increase in liver weight, lesions in spleen and kidneys. LOAEL was 891 mg/kg bw/day.

Ref.: 17

Subchronic toxicity was evaluated in groups of 5 rats (sex and strain not reported) administered DEGBE in drinking water for 30 days at a level of 0, 0.051, 0.094, 0.21, 0.65, 0.97 or 1.83 ml/kg/day. There were no compound-related mortalities. Clinical observations included decreased water consumption and slightly retarded growth at levels at and above 0.21 ml/kg/day. Necropsy revealed abnormalities with the adrenals, small intestine, heart, kidney, liver, leg muscle, pancreas, spleen and testicles.

Ref.: 18

Subchronic oral toxicity was evaluated in 3 groups of 10 male albino Charles River rats administered DEGBE by gavage at dose levels equivalent to 1/2, 1/4 and 1/8 of the acute LD_{50} (actual dose levels not reported) 5 days/week for 6 weeks. An additional group of 10 rats was used as a control. No compound-related mortality was observed. Clinical signs of toxicity in rats at the highest dose level included bloody urine, dyspnea, prostration, unkempt hair, and blood around the nose and mouth. A significant ($p < 0.05$) reduction in weight gain was observed in the highest dose group, while relative spleen and liver weights were significantly ($p < 0.05$) increased in the 2 highest dose levels. Haematological evaluation revealed decreased haemoglobin concentration and total red cells at the 2 highest dose levels. Gross necropsy revealed blood in the urinary bladder and dark, enlarged spleens in rats at the highest dose level. Histopathologic examination revealed splenic congestion, hypocellularity, and hemosiderin-like pigmentation in all treatment groups.

Ref.: 19

Dermal, rabbit
NZW rabbits, groups of 3 males and 3 females received 0 and 2 ml/kg bw/d (1.5%; 30 mg/kg bw/day) 7 hrs/day, 5 days/wk for 4 wk with DEGBE (non-occluded). No local or systemic effects were observed.

Ref.: 20

Inhalation, rat
F344 rats, groups of 15 males and 15 females received 0, 13, 39, and 117 mg/m^3 DEGBE 6 hrs/day, 5 days/wk for 5 wk. In males of the mid and high dose group the relative liver weight had a dose-related decrease. Hepatocyte vacuolisation consistent with fatty change and increased relative liver weight was observed in females of the high dose group. This effect was also observed in the females of the control and other treatment groups, but it was less intense. In the high dose group 3/10 females had a pale liver.

Ref.: 21

Wistar rats, groups of 5 males and 5 females received 0, 100 (vapour), 350 (aerosol), and 1000 mg/m^3 DEGBE 6 hrs/day, 5 days/wk for 2 wk (no recovery). Perivascular and peribronchial infiltrate in male and female and decreased spleen weight in males at all doses. Increased lung weight was observed at the two highest doses.

Ref.: 22

Wistar rats, groups of 10 females received 0 and 350 (aerosol) mg/m^3 DEGBE 6 hrs/day, 5 days/wk for 2 wk followed by a 4 wk recovery period. No effects were recorded.

Ref.: 23

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

Oral, rat
F344 rats, groups of 16 males received 0, 65, 327, and 1630 mg/kg bw/day of DEGBE by gavage for 7 d/wk for 13 wk. A slight increase in liver weight and a dose-related increase in creatinine were found in all dosed groups. The spleen weight was also increased in the mid dose group. The bodyweight was reduced in the high dose group. Very high mortality, 88%, occurred in the high dose group. The mortality at the mid dose was 60%. It cannot be excluded that the high mortality was caused by irritation of the forestomach. LOAEL was 65 mg/kg bw/day.

Ref.: 24

F344 rats, groups of 16 females received 0, 51, 254, and 1270 mg/kg bw/day of DEGBE by gavage for 7 d/wk for 13 wk. A slight decrease in lymphocytes was found in all dosed groups. The bodyweight was reduced in the high dose group. Very high mortality, 92%, occurred in the high dose group. The mortality at the mid dose was 30%. It cannot be excluded that the high mortality was caused by irritation of the forestomach. LOAEL was 51 mg/kg bw/day.

Ref.: 24

Comment
There are doubts on the quality of the study reported in ref 24 because of the high, unclarified mortality.

F344 rats, groups of 10 males and 10 female received 0, 50, 250, and 1000 mg/kg bw/day of DEGBE drinking water for 13 wk. No treatment related effect was found at the low dose. An equivocal decrease in RBC, Hb and Hct were found at 250 mg/kg bw/day. In the high dose group, the bodyweight was decreased by 4% and the relative liver weight increased by 7 – 10%. In addition slight increase in several P450 and UDP-glucuronosyl transferase and

slight decrease in total proteins, cholesterol, and amino transferase was observed. Minor histopathological changes in the liver of female rats. No effects on sperm motility, morphology, sperm counts, or testis histopathology were observed. NOAEL was 250 mg/kg bw/day. The liver was the primary target of toxicity.

Ref.: 25

Dermal, rat

SD rats, groups of 12 males and 12 females received 0, 0.2, 0.6, and 2 ml/kg bw/d (0, 190, 580, and 1900 mg/kg bw/day) 6 hrs/day, 5 days/wk for 13 wk with DEGBE (occluded). No systemic or neurotoxic effects were observed in the group of low- or mid-dosed groups. Renal tubular epithelium degeneration was found in 2 high-dosed males. NOAEL was 580 mg/kg bw/day.

Ref.: 26

Guideline:	/
Species/strain:	Sprague-Dawley rats
Group size:	10 males and 10 females
Test substance:	DEGBE
Batch:	/
Purity:	99.5 – 99.8%
Dose levels:	0, 10%, 30%, and 100%, 2ml/kg bw (0, 200, 600, and 2000 mg/kg bw/d)
Route:	Dermal under occlusion
Exposures:	13 weeks, 5 h/d, 5d/w
GLP:	/

Sprague-Dawley, groups of 10 males and 10 females, received 2ml/kg bw of a 0, 10, 30, and 100% solution of DEGBE (0, 200, 600, 2000 mg/kg bw/d) dermally under occlusion 5 h/d, 5d/w for 13 weeks. DEGBE was applied to a 3 x 3 cm area on the clipped skin of the back. Qualitative dermal evaluation and detailed clinical evaluation were conducted each treatment day. There was no mortality in any of the groups. Body weights and feed consumption were not adversely affected by the DEGBE treatment. Clinical observation during the study revealed one mid-dose and one high-dose female with hematuria or red urinary staining on the haircoat, first seen at week 7 of the study. Urine analyses at the end of the study revealed a slightly increased incidence of occult blood in the urine of females treated with 30 or 100% DEGBE. No increased numbers of erythrocytes were seen on microscopic examination. Evaluation of the application sites revealed dermal irritation, which was concentration-dependent. Microscopic examination of skin sections from the application site revealed no DEGBE-related histological changes.

Ref.: 27

DEGBE was tested for neurotoxicity in Sprague-Dawley rats (12/sex/concentration group) exposed dermally to concentrations of 0, 10, 30, or 100% DEGBE dissolved in distilled water, at a volume of 2 ml/kg bw, 6 hours/day, 5 days/week for 13 weeks. The rats were examined in a functional observation battery at 0 and 24 hours, and 7, 14, 35, 63, and 91 days after the first exposure period; rats also received motor activity testing on study days 34, 62, and 90. At study termination, 6 rats each in the control and high-concentration group were perfused for neuropathological examinations. Treatment had no adverse effects with respect to survival, body weight gain, food consumption, or clinical signs. Five high-dose females had scab formation at the application site. Functional observational battery performance, motor activity, and neuropathology were normal in treated rats. Two high-concentration males had mild degeneration of the renal tubular epithelium; the authors considered the significance of this finding to be equivocal.

Ref.: 28

Inhalation, rat

Wistar rats, groups of 10 males and 10 females received 0, 13, 40, and 94 mg/m^3 DEGBE 6 hrs/day, 5 days/wk for 90 days followed by a 4 wk recovery period. No effects were recorded. NOAEL was 94 mg/m^3.

Ref.: 29

General comment
A NOAEL of 250 mg/kg bw/d has been determined from a 13-week drinking water study with rats. The value is based on decreased bodyweight (4%) and increased relative liver weight (7 – 10%) in the higher dose group.

3.3.5.3. Chronic (> 12 months) toxicity

No data found.

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

The *in vitro* genotoxicity of DEGBE has been studied in several experiments. The results are summarized in Table 3.2.

Table 3.2. *In vitro genotoxicity of DEGBE*

Endpoint/Organism	Strain or type/Target	Concentration	Result	Remark	Reference
Gene mutation					
Salmonella typhimurium	TA98, TA100 TA1535, TA1537, TA1538	Up to 20 μl/plate	-ve	+/-S9	30, 31, 32, 33
CHO cell	HGPRT locus	100-5000 μg/ml	-ve	+/-S9	34
Mouse lymphoma cell	L5178Y TK+/-	0.42-7.5 μl/ml	Weakly +ve (-S9)	+/-S9	30
Chromosome aberration					
CHO cell		4.5-7.9 μl/ml	-ve	+/-S9	30
Unscheduled DNA synthesis					
Rat hepatocytes	Primary	0.26-4.4 μl/ml	-ve	Grain counts	30

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

The *in vivo* genotoxicity of DEGBE has been studied in two experiments. The results are summarized in Table 3.3.

Table 3.3. *In vivo genotoxicity of DEGBE*

Endpoint/Organism	Strain or type/Target	Concentration	Result	Remark	Reference
Sex-linked recessive lethal mutations					
Drosophila melanogaster	Maturing germinal cells	Feeding 11000 mg/l, 3d Injection 0,3 µl of 14000 mg/l	-ve -ve		30
Micronucleus frequency					
Mouse, CD-1, 5M, 5 F	Bone marrow	330, 1100, and 3300 mg/kg bw, 1 x oral gavage	-ve	Mice killed at 24, 48, and 72 hrs	34

General comment
DEGBE has been tested for genotoxicity *in vitro* in the Salmonella test as well as for gene mutations in mouse lymphomas cells ($tk^{+/-}$) and mutations (*hprt*-locus) and chromosome aberration in Chinese hamster ovary cells, and unscheduled DNA synthesis in primary rat hepatocytes. In addition it has been tested for increased micronucleus frequency in CD-1 mice and sex-linked recessive lethal mutations in *Drosophilia melanogaster.* All the tests were negative with the exception of mutations in mouse lymphoma cells which were weakly positive in the absence of S-9, while it was negative in the presence of S-9. It is concluded that DEGBE do not have relevant mutagenic potential *in vivo*.

3.3.7. Carcinogenicity

No data submitted

3.3.8. Reproductive toxicity

Oral, mice

Guideline: /
Species/strain: Swiss CD-1 mice
Group size: 50 pregnant mice
Test substance: DEGBE
Batch: /
Purity: >99%
Dose levels: 500, and 2050 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 DEGBE (>99% purity) by gavage at 500 mg/kg/day (calculated LD_{10} 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. None of the dams died, maternal weight gain was not reduced and, of 37 surviving pregnant females, there were 36 viable litters (97%) compared with 97% control litter viability. No external malformations were seen, pup survival to PND was unaffected and no other indication of specific developmental toxicity was found. 25% maternal mortality occurred at the high dose (2050 mg/kg bw/d). No embryo- or foetotoxicity were noted.

Ref.: 35, 36

Reproductive toxicity was evaluated in groups of 10 pregnant Charles River CD female mice receiving an oral gavage dose of DEGBE at 10 ml/kg body weight on gestation days 7 through 14. Maternal mortality, clinical observations and gross necropsy were not reported. There was a significant reduction ($p < 0.05$) in the number of live pups per litter, reduced survival, and reduced birth weight among offspring of treated dams.

Ref.: 37

Rat

Guideline:	/
Species/strain:	CD rats
Group size:	25 males and 25 females
Test substance:	DEGBE
Batch:	/
Purity:	95±2%
Dosage:	0, 250, 500, and 1000 mg/kg bw/d
Route:	Gavage
Exposures:	Males 60 days prior to mating and until end of mating period. Females 14 days prior to mating until sacrificed on day 13 of gestation or at day 21 of lactation.
GLP:	/

A one-generation reproduction was performed in CD rats given doses of 0, 250, 500, and 1000 mg/kg bw/day by gavage. Untreated males were mated with treated females and vice versa. All groups consisted of 25 rats. No signs of parental toxicity or effects on fertility were observed when the males were treated 60 days prior to mating and until end of mating period. The females were treated from 14 days prior to mating until sacrificed on day 13 of gestation or at day 21 of lactation. Reduced body weight of the pups from the high-dose females was the only treatment-related effect. The number of liveborn pups was slight, but not statistically significantly decreased at 1000 mg/kg bw/day. It was concluded that NOAEL for development effect was 500 mg/kg bw/day and for parental toxicity and fertility 1000 mg/kg bw/day.

Ref.: 38

Wistar rats, groups of 14 – 16 females were given 0, 25, 115, and 633 mg/kg bw/d (gavage) during day 0 – 20 of gestation. According to the authors reduction in body weight gain was observed at all dose levels and was the only sign of maternal toxicity. No effect on developmental toxicity or teratogenic effects were observed. There were a statistical insignificant decrease in number of implants (10.4 ± 1.1, 10.7 ± 1.4, 9.4 ± 0.5, 8.8 ± 1.3) and new-borns (9.6 ± 1.5, 10.3 ± 1.6, 8.6 ± 0.9, 8.2 ± 0.8) per litter is probably not a substance-related effect because of the high variability.

Ref.: 39

Dermal, rat

Guideline:	/
Species/strain:	Sprague-Dawley rats

Group size:	25 males and 25 females
Test substance:	DEGBE
Batch:	/
Purity:	99.5 – 99.8%
Dosage:	0, 100%, 2ml/kg bw (0, 2000 mg/kg bw/d)
Route:	Dermal under occlusion
Exposures:	13 weeks, 5 h/d, 5d/w
GLP:	/

Sprague-Dawley, groups of 25 males and 25 females, received 2 ml/kg bw of a 0 and 100% solution of DEGBE (0, 2000 mg/kg bw/d) dermally under occlusion 5 h/d, 5d/w for 13 weeks. The rats were subsequently mated and the treatment of the females continued through day 20 of gestation and allowed to deliver and nurse their offspring through day 21 lactation (weaning). DEGBE was applied to a 3 x 3 cm area on the clipped skin of the back. There was no evidence of histopathologic changes in the testes, and vaginal cytology indicated no adverse effect on oestrous cycling. There were no effects on reproductive performance of the DEGBE-treated males and females. Litters delivered by treated females contained the same number of live pups as control litters and the growth and survival of pups within the treated litters was comparable to control. No reproductive or systemic toxicity was observed at 2000 mg/kg bw/d.

Ref.: 27

Rabbit

Guideline:	/
Species/strain:	Female New Zealand White rabbits
Group size:	20 pregnant rabbits
Test substance:	DEGBE
Batch:	/
Purity:	95 ± 2%
Dosage:	0, 100, 300, 1000 mg/kg bw/d
Route:	Dorsal skin, 4 hr/d
Exposures:	Pregnant rabbits, days 7 through 18 of gestation
GLP:	/

NZW rabbits, group of 20 pregnant females, received 0, 100, 300, and 1000 mg/kg bw/d DEGBE 4 hr/d from gestation day 7 – 18 (non-occluded). The rabbits were sacrificed on day 29 of gestation. All the dams treated with DEGBE gained less weight than the controls during gestation, although only the difference for the group treated with 300 mg/kg bw was statistically significant. The lack of dose response in the treated groups suggested that the lower weight gain was not directly related to the amount of DEGBE absorbed. The two high dose levels caused skin irritation after about one week, which persisted until the end of the study. There were no indications for developmental or teratogenic effects at any of the dose levels tested.

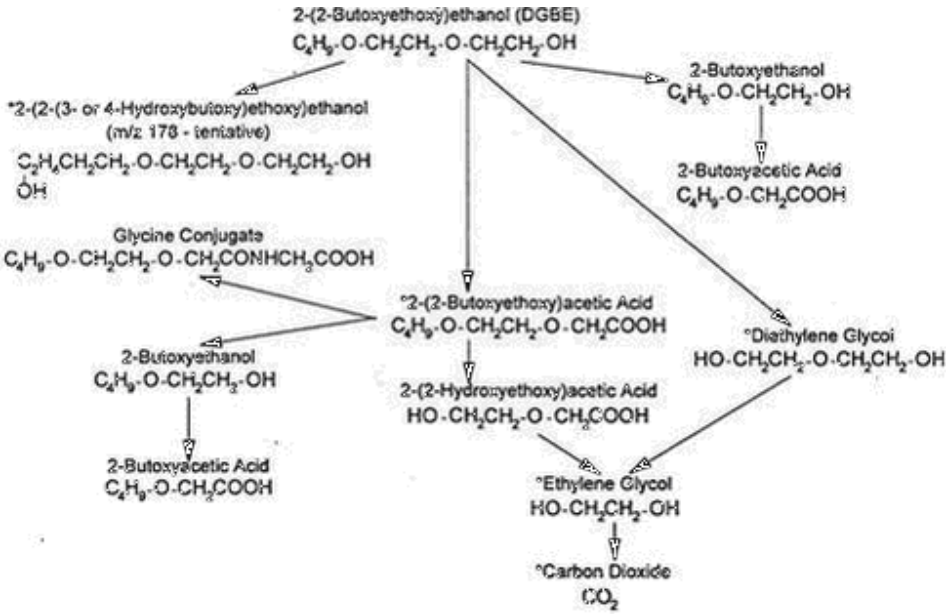
Ref.: 38

General comments

In a one-generation gavage study by rats the NOAEL for fertility was 1000 mg/kg bw/d (highest dose level tested). As for developmental effects, the oral NOAEL was established at 500 mg/kg bw/d. The only effect observed at the next higher dose level tested was reduced body weight gain of the pups. DEGBE caused no teratogenic effects. No effects were observed in a dermal one-generation study of rats at a dose of 2000 mg/kg bw/d. Neither systemic maternal toxicity nor developmental or teratogenic effects were observed in rabbits dermally exposed to dose levels up to 1000 mg/kg bw/d.

3.3.9.	Toxicokinetics

DEGBE is excreted primarily in urine following oral, dermal or parenteral administration to rats. The major metabolite is 2-(2-butoxyethoxy)acetic acid (BEAA).



A proposed metabolic pathway for DEGBE in the rat according to Deisinger & Guest (1989 – from DECOS 1996).

Ref.: 12, 40, 41, 42

3.3.10.	Photo-induced toxicity

3.3.10.1.	Phototoxicity / photoirritation and photosensitisation

/

3.3.10.2.	Phototoxicity / photomutagenicity / photoclastogenicity

/

3.3.11.	Human data

There is a case report which describes kidney and liver damage in two people who worked in a closed room with paint containing DEGBE and, at the same time, consumed large quantities of alcoholic beverages.

Ref.: 43

3.3.12.	Special investigations

No data submitted.

3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

Diethylene glycol monobutyl ether
DEGBE

The safety calculation is only considering dermal exposure.

Maximum dermal absorption of test substance considered being 50%

NOAEL based on liver toxicity and reduced bodyweight in rats was 250 mg/kg bw/d

Exposure 35 ml/week, 9% DEGBE. Retention 0.1; = 315 mg

Maximum absorption through the skin per treatment	315 x 50/100	=	157.5 mg
Typical body weight of human		=	60 kg
Systemic exposure dose (SED)	157.5/60	=	2.6 mg/kg
No observed adverse effect level (mg/kg) (13 week drinking water, rat)	NOAEL	=	250 mg/kg
Margin of Safety	**NOAEL / SED**	**=**	**96**

The value of MOS equal to 96 is considered to give sufficient protection in relation to the use of DEGBE as solvent in hair dye preparations.

3.3.14. Discussion

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 monobutyl ether (DEGBE) is not reported. The physico-chemical characterisation and purity of the substance is not reported in several studies.

General toxicity
DEGBE is excreted primarily in urine following oral, dermal or parenteral administration to rats. The major metabolite is 2-(2-butoxyethoxy)acetic acid (BEAA).

DEGBE has low acute toxicity by oral and dermal routes. The available data do not allow a definite conclusion on acute toxicity of DEGBE by inhalation.

In oral studies DEGBE caused effects in liver, spleen, kidneys and haematological parameters. A NOAEL of 250 mg/kg bw/d has been determined from a 13-week drinking water study with rats. The value is based on decreased bodyweight (4%) and increased relative liver weight (7 – 10%) in the higher dose group.

Human exposure – 2 ml/kg has produced cyanosis, tachypnea, and slight uremia.
There is a case report which describes kidney and liver damage in two people who worked in a closed room with paint containing DEGBE and, at the same time, consumed large quantities of alcoholic beverages.

Irritation /sensitisation
DEGEE is moderately irritant to the eye and slightly irritating to the skin. No conclusion on sensitisation can be drawn due to lack of information in relation to the available experiment.

Reproductive toxicity
In a one-generation gavage study by rats the NOAEL for fertility was 1000 mg/kg bw/d (highest dose level tested. As for developmental effects the oral NOAEL was established at 500 mg/kg bw/d. The only effect observed at the next higher dose level tested was reduced body weight gain of the pups. DEGBE caused no teratogenic effects. No effects were observed in a dermal one-generation study of rats at a dose of 2000 mg/kg bw/d. Neither systemic maternal toxicity nor developmental or teratogenic effects were observed in rabbits dermally exposed to dose levels up to 1000 mg/kg bw/d.

Dermal absorption
None of the available studies comply with accepted guideline and GLP. In the EU Risk Assessment Report (ref.: 1) it was concluded: *"From the dermal studies it is concluded that complete dermal absorption cannot be excluded. For risk characterisation 100% dermal absorption should be assumed (worst-case estimate)."* In Submission, the French Authorities states: *"Because no reliable data are available on skin absorption, it is assumed that the entire amount applied to the skin is absorbed."* However, based on the experiments reported above and well-conducted dermal absorbance study with EGBE and DEGEE (see Opinion 1045/06 and 1044/06 by SCCP) it is unlikely that the dermal absorption is larger than 50%.

Mutagenicity
DEGBE has been tested for genotoxicity *in vitro* in the Salmonella test as well as for gene mutations in mouse lymphomas cells (TK+/-) and mutations (*hprt*-locus) and chromosome aberration in Chinese hamster ovary cells, and unscheduled DNA synthesis in primary rat hepatocytes. In addition it has been tested for increased micronucleus frequency in CD-1 mice and sex-linked recessive lethal mutations in *Drosophila melanogaster.* All the tests were negative with the exception of mutations in mouse lymphoma cells which were weakly positive in the absence of S-9, while it was negative in the presence of S-9. It is concluded that DEGBE do not have relevant mutagenic potential *in vivo*.

Carcinogenicity
No carcinogenicity study is available.

4. CONCLUSION

Based on the information provided, the SCCP is of the opinion that the use of diethylene glycol monobutyl ether (DEGBE) as a solvent in hair dye formulations at a concentration up to 9.0% does not pose a risk to the health of the consumer.

The opinion relates to the direct application to the hair/scalp. It does not include any other cosmetic exposure, such as exposure from other types of cosmetics or possible aerosol/spray products.

5. MINORITY OPINION

Not applicable

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