EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Consumer Products

SCCP

OPINION ON

Diethylene glycol

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCCP adopted this opinion at its 16th plenary of 24 June 2008

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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http://ec.europa.eu/health/ph_risk/risk_en.htm

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1. BACKGROUND

Diethylene glycol (DEG) (CAS 111-46-6) is listed in the Inventory with functions as solvent, viscosity controlling and masking/perfuming. Furthermore, it is listed in section II, perfume and aromatic raw materials.

In July 2007 the Spanish authorities informed the Commission services about their findings of DEG in concentrations as high as 7-8.3% in toothpaste products.

Following these findings also in other Member States, information including risk assessment of DEG in tooth paste and oral hygiene products has been provided by the Spanish, the French and the Swiss Authorities.

The French authorities have at the same time proposed a regulation i.e. a ban of DEG as ingredient in oral hygiene products and a limitation of DEG as a residue in glycerol of up to max 0.1% and for polyethylene glycols a residue content of diethylene glycol of up to 0.4% for the sum of diethylene glycol and ethylene glycol.

COLIPA[1] has informed the Commission Services by letter primary October 2007 " … that DEG is not intentionally added as an ingredient to oral care products. However, DEG can be present as an impurity in glycerol and polyethylene glycols, which are common ingredients in oral care products". COLIPA also submitted an evaluation: "Risikobewertung zu Diethylenglycol in Zahnpasta" done by the BfR[2] and proposes a similar regulation as the French Authorities.

In literature, several reported cases of death after the intake of glycerol contaminated by DEG has been reported.

The European Pharmacopoeia defines limits for DEG in glycerol (0.1% DEG) and polyethylene glycols (0.4% sum of ethylene glycol and DEG).

DG ENTR has asked Industry to submit data, if they would like to defend the continued use of DEG as an ingredient in cosmetic products.

2. TERMS OF REFERENCE

1. *Does SCCP consider that a limit for the safe use of DEG as an ingredient in cosmetic products including oral care products can be set taken into account the provided risk assessments and the fatal cases reported in the enclosed literature?*

2. *If no safe limit for DEG as an ingredient in cosmetic products can be set, and taken into account that DEG exists as an impurity in commonly used cosmetic ingredients like glycerine and polyethylene glycols, does SCCP consider a maximum concentration up to 0.1% of DEG in a finish cosmetic product as safe?*

[1] COLIPA - The European Cosmetic Toiletry and Perfumery Association
[2] BfR - Federal Institute for Risk Assessment, Germany

3. OPINION

Information without specific reference is taken from the HSDB on diethylene glycol.

Ref.: 1

3.1. Chemical and Physical Specifications

3.1.1.	Chemical identity

3.1.1.1.	Primary name and/or INCI name

Diethylene glycol

3.1.1.2.	Chemical names

2,2'-Oxybisethanol
Diglycol
Ethanol, 2,2'-oxybis-
1,5-Dihydroxy-3-oxapentane
2-(2-Hydroxyethoxy)ethanol
2,2'-Dihydroxyethyl ether
2,2'-Dihydroxydiethyl ether
2,2'-Oxyethanol
2,2'-Oxydiethanol
3-Oxapentamethylene-1,5-diol

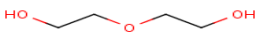
3.1.1.3.	Trade names and abbreviations

DEG
Caswell No. 338A
Deactivator E
Dicol
Digenos
Diglycol
Digol
Dihydroxydiethyl ether
Dissolvant APV

3.1.1.4.	CAS / EINECS number

CAS: 111-46-6
EINECS: 203-872-2

3.1.1.5.	Structural formula



3.1.1.6.	Empirical formula

$C_4H_{10}O_3$

3.1.2.	Physical form

Colourless syrupy liquid

3.1.3.	Molecular weight

Molecular weight: 106.12

3.1.4.	Purity, composition and substance codes

Available as 100% product

3.1.5.	Impurities / accompanying contaminants

Acidity (as acetic acid, max) 0.005%, water (max) 0.2%, ash (max) 0.005 g/10 ml

3.1.6.	Solubility

Miscible with water, alcohol, ether, acetone, ethylene glycol;
Insoluble in benzene, toluene, carbon tetrachloride

3.1.7.	Partition coefficient (Log P_{ow})

Log P_{ow}: - 1.47 (estimated)

3.1.8.	Additional physical and chemical specifications

Appearance:	Colourless syrupy liquid
Odour:	Practically odourless
Taste:	Sharply sweetish taste
Melting point:	-6.5°C
Boiling point:	244 – 245 °C
Density:	1.18 at 20 °C
Rel. vap. density:	3.66 (air=1)
Vapour Pressure:	$5.7x10^{-3}$ mm Hg at 25 °C

3.1.9.	Stability

DEG is highly hygroscopic.

3.2. Function and uses

Diethylene glycol was discovered in 1869. The commercial production did not begin until 1928. It proved to be an excellent solvent and was used as a glycerol substitute, as a moistening agent, and in the production of resins and explosives. Its use in food products, however, was not permitted because of the paucity of scientific data proving its safety for oral administration.

It is an intermediate in production of polymers and triethylene glycol, used in antifreeze, natural gas dehydration, textile conditioning, and as humectant for tobacco.

DEG is listed in the Inventory of Cosmetic Ingredients with functions as solvent, viscosity controlling and masking/perfuming. Furthermore, it is listed in section II, perfume and aromatic raw materials.

Most of the intoxications with DEG have been produced by the ingestion of contaminated medicines.

DEG was in 1985 detected in wines from Austria and Germany. DEG had been added as a sweetener. No poisoning was detected, but a million of bottles were removed from the marked.

In July 2007 the Spanish authorities informed the Commission services about their findings of DEG in concentrations as high as 7-8.3% in toothpaste products.

3.3. Toxicological Evaluation

Before the elixir disaster in 1937 (see section 3.3.11), only two studies had been done on the toxicity of DEG. In 1931, Von Oettingen and Jiroucli determined that the minimum lethal dose of DEG in mice was *5* ml/kg bw/day of a 50% solution given subcutaneously. Histological analyses showed marked hydropic degeneration of the kidney. In early 1937, Ambose reported that ingestion of a 3% DEG solution was fatal in a rat model.

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

LD50 rat:	15.6 g/kg bw/day
LD50 mouse:	13.3 g/kg bw/day
LD50 rabbit:	26.9 g/kg bw/day
LD50 guinea pig:	14.0 g/kg bw/day
LD50 cat:	3.5 g/kg bw/day
LD50 dog:	9.0 g/kg bw/day

3.3.1.2. Acute dermal toxicity

/

3.3.1.3. Acute inhalation toxicity

LC50 mouse: 130 mg/m^3/24 h

3.3.2. Irritation and corrosivity

3.3.2.1. Skin irritation

DEG is not irritating to skin

3.3.2.2. Mucous membrane irritation

DEG tested by application of a drop to rabbit corneas is found not injurious, and tests on excised bovine corneas have shown that it does not alter the adhesion of epithelium to stroma.

3.3.3. Skin sensitisation

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3.3.4. Dermal / percutaneous absorption

Dermal absorption is estimated to be about 10%

Ref.: 2

Comment
No information about how this dermal absorption value was estimated is available. Therefore, SCCP will use 100 % dermal absorption in the risk considerations.

3.3.5. Repeated dose toxicity

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

/

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

Most animal studies on DEG are 30 – 50 years old. The observed NOELs in these studies are between 50 and 2350 mg/kg bw/day in rats. In these old studies, no information is given concerning possible contamination by ethylene glycol.

No biological effects were observed when rats received 1% DEG in the feed (about 1000 mg/kg bw/day.

Ref.: 3

Groups of 15 male and 15 female Wistar rats received feed containing 0, 0.4, 2 and 4% DEG for 99 days. Six rats receiving 4% DEG in their feed died. Kidney damage with hydropic degeneration and kidney tubular necroses occurred. Calcium oxalate crystals were found in the urinary bladder. Increased liver size with hydropic degeneration was also found. One male rat receiving 2% DEG in the feed also developed kidney damage.

Ref.: 4

In another study, groups of 10 male and 10 female Wistar rats received 0.085, 0.17, and 2.0% DEG in the feed for 225 days. Oxalate crystals were found in the kidneys at 0.17% DEG (100 mg/kg bw/day). Kidney damage was observed at higher doses. It was assumed that the kidney damage was due to a result of the formation of oxalate crystals and that the kidney was the primary target organ. Effects in the liver were assumed to be due to secondary unspecific effects. Stones in the urinary bladder were observed at high doses. It was concluded that the NOAEL was 50 mg/kg bw/day.

Ref.: 4

3.3.5.3. Chronic (> 12 months) toxicity

A long term rat feeding study showed that 1% DEG in the diet over a two year period resulted in slight growth depression, a few calcium oxalate bladder stones, minimal kidney damage, and occasional liver damage. At 4% dietary level, there was increased mortality, a marked depression of growth rate, bladder stones, severe kidney damage, and moderate liver damage. Bladder tumours, mostly benign, occurred at 1,500 and 3,000 mg/kg/day in male rats treated with DEG; these tumours were associated with irritation from bladder stones which occurred at those doses.

Ref.: 3, 5

DEG containing only 0.031% of ethylene glycol was fed to weanlings, 2 month old, and 1 year old rats for up to 2 years at levels of 4.0 and 2.0% in a laboratory chow. Although the weanling rats developed more bladder stones than the other groups, the difference was

insignificant. The yearling rats developed their bladder stones somewhat earlier. The highest stone formation was 8 in 20 (40%) rats at the 4% dosage level. None was found in the rats fed the 2% level which is contrary to the conclusions of the previous study. The results indicate that DEG substantially free of ethylene glycol does not cause bladder stones, suggesting that it is not metabolized to any great degree to ethylene glycol.

Ref.: 1

General comment

The data on repeated toxicity of DEG are old and it cannot be excluded that the presence of ethylene glycol as impurity in the DEG may have influenced the results. Thus, while calcium oxalate crystals were found in the rat bladder in a 225 day experiment at 100 mg/kg bw/day (ref. 4), bladder stones were not observed at more than 1000 mg/kg bw/day in another study with DEG containing only 0.031% ethylene glycol.

The French authority (ref. 6) points out that data on toxicity with DEG are rare in the scientific literature and that DEG and ethylene glycol have similar toxicity. However, quantitatively, DEG is less toxic than ethylene glycol. As a result, in the first instance, they used the dose-effect correlations relating to ethylene glycol to propose a Toxicity Reference Value (TRV) for DEG. Given that the critical effect of ethylene glycol at repeated doses is renal tubular damage, and that the NOAEL in the most sensitive species (rat) is 200 mg/kg/day (Ref. 7), applying factors of uncertainty of 10 for the rat-to-man extrapolation and a factor of 10 to take account of interpersonal variability in humans (i.e. 100 in total) led to the proposal of a TRV of 2 mg/kg bw/day.

SCCP is of the opinion that for a safety assessment based on animal experiments, a NOAEL of 50 mg/kg bw/day (formation of calcium oxalate crystals in the rat bladder) (ref. 4) may be used. Since NOAEL in rat for ethylene glycol was 200 mg/kg bw/day, it seems unlikely that the presence of ethylene glycol as impurity in DEG should give a NOAEL lower than for ethylene glycol itself.

3.3.6. Mutagenicity / Genotoxicity

3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

DEG was evaluated for mutagenicity in the Salmonella/microsome preincubation assay using a standard protocol approved by the National Toxicology Program. DEG was tested at doses of 0, 100, 333, 1000, 3333, and 10,000 µg/plate in four Salmonella typhimurium strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aroclor-induced rat or hamster liver S9. DEG was negative in these tests and the highest ineffective dose level tested in any Salmonella tester strain was 10,000 µg/plate.

The results of *in vitro assays* of DEG for chromosomal aberrations and in sister chromatid exchange assays have also been uniformly negative.

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

In a Memorandum from US Environmental Protection Agency dated 30 June 2006 it was stated that DEG did cause chromosomal damage in bone marrow cells. No reference or further information was given.

3.3.7. Carcinogenicity

See Section 3.3.5.3

3.3.8. Reproductive toxicity

3.3.8.1. One generation reproduction toxicity

Mice

DEG was tested for reproductive toxicity in Swiss CD-1 mice using the RACB protocol. It was part of a large structure-activity test series of glycol ethers and congeners evaluated using this design. F_0 mice were exposed to drinking water containing 0.0, 0.35%, 1.75%, and 3.5% DEG. Based on water consumption data collected during the study, these concentrations produced calculated DEG consumptions of about 612, 3062, and 6125 mg/kg bw/day.

While F_0 body weight was unchanged by DEG consumption during the mating period, the number of litters per pair was reduced by 12% at the top dose, and the number of live pups/litter was reduced by 32%. Pup weight adjusted for litter size was reduced by about 12% at the top dose level. In a crossover mating to determine the affected sex, number of pups/litter was equivalent across the three groups, but adjusted pup weight was reduced by 10% in the control male x 3.5% DEG female mating. After the F_1 mice were weaned, the control and 3.5% DEG F_0 mice were killed and necropsied. There were no treatment-related changes in male organ weights or histopathology, while female body weight was reduced by 7% after 3.5% DEG consumption. Adjusted organ weights were unchanged.

For the F_1 mating trial, exposed mice from the 1.75% group were used, because insufficient mice were available from the top dose, due to reduced fertility in that group. DEG at 1.75% did not affect pup survival to mating at postnatal day 74. There were no treatment-related alterations in the number or weight of F_2 pups in the Task 4 mating trial. After all the F_2 litters were born and the F_1 females subjected to oestrous cyclicity evaluation, the F_1 mice were killed and necropsied. There was an 11% and 7% decrease in the body weights of the treated males and females, respectively. No organ weights were affected, nor were sperm indices changed.

In summary, diethylene glycol at 3.5% was a reproductive toxicant in Swiss mice, based on reductions in litters/pair, and in mean litter size. In F_0 mice, this was unaccompanied by body weight loss, while in F_1 mice, there was reduced body weight in the absence of a fertility effect. No effects were observed at 0.35% (612 mg/kg bw/day).

Ref.: 8

Reproductive toxicity was evaluated in groups of 10 pregnant Charles River CD female mice receiving an oral gavage dose of diethylene glycol at 10 ml/kg body weight on gestation days 7 through 14. Maternal mortality, clinical observations or 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 the offspring of treated dams.

Ref.: 9

3.3.8.2. Teratogenicity

Mice

This study was conducted to assess the potential for orally administered DEG to cause developmental toxicity. The oral route of administration corresponds to the most hazardous potential human route of exposure to DEG. The CD-1 mouse was selected as the test animal for this study based on evidence for DEG-induced teratogenicity in the CD-1 mouse reported by the National Toxicology Program in a continuous breeding study, as well as the paucity of developmental toxicity data.

DEG was administered by gavage to timed-pregnant Swiss (CD-1) mice (26-31 per group) on gestational days (GD) 6-15 at dose levels of 0, 1250, 5000, or 10,000 mg/kg bw/day. Animals were observed daily for clinical signs of toxicity. Food and water consumption and body weights were determined on GD 0, 3, 6, 9, 12, 15, and 17. All animals were killed on GD 17 and examined for maternal body and organ weights, implant status, foetal weight, sex, and morphological development.

Maternal body weights did not differ significantly between the control group and any of the DEG-treated groups. Relative water intake was significantly increased over control for every interval starting at GD 6 in the 5000 and 10,000 mg/kg bw/day DEG treated animals. Maternal animals given 10,000 mg/kg bw/day of DEG had significantly decreased relative (g/kg bw/day) food consumption from GD 6 to 12.

One maternal animal treated with 10,000 mg/kg bw/day of DEG was sacrificed in extremis on GD 10. Necropsy and histopathologic examinations revealed evidence of renal degeneration and suggested that morbidity was due to toxicity produced by DEG. Necropsy of maternal animals on GD 17 showed that animals from the 5000 and 10,000 mg/kg bw/day DEG groups had significantly increased absolute (g) and relative (% body weight) kidney weights when compared to control animals. 11% (3/28) of the pregnant females at the high dose showed evidence of renal pathology as compared to 0/20 pregnant females from the vehicle control group.

No effects of DEG were observed on pre- or post-implantation loss. The mean foetal body weight per dose group on GD 17 was associated with a significant decreasing linear trend (99%, 96%, and 85% of control from the low to high dose) and mean foetal body weight was significantly decreased in the high dose group (0.865 g) when compared to controls (1.012 g). Examination of the foetuses for external, visceral and skeletal malformations did not reveal any significant effects between dose groups. The decrease in foetal body weight indicated developmental toxicity at the 10,000 mg/kg bw/day exposure level of DEG.

In summary, there was no maternal or developmental toxicity at 1250 mg/kg bw/day of DEG. The mid-dose (5000 mg/kg bw/day DEG) produced significant maternal toxicity, but no clear evidence of developmental toxicity. The high dose (10,000 mg/kg bw/day DEG) caused the death of 1 out of 28 pregnant dams, maternal toxicity and developmental toxicity

Ref.: 10

Guideline:	/
Species/strain:	Virgin male and virgin female Crl: CD-1 (ICR) BR mice
Group size:	30 timed pregnant females per dose
Test substance:	Diethylene glycol
Batch:	TFJ-44408 PL26032
Purity:	99.87%, [ethylene glycol 0.02%, triethylene glycol 0.11%]
Dose level:	0.0 (controls) 0.5, 2.5 or 10 ml/kg bw/day (equivalent to 0, 559, 2795, and 11,180 mg/kg bw/day
Route:	Oral, gavage
Observation:	18 gestation days
GLP:	

Based on the probe study, groups of 30 timed-pregnant CD-1 mice were dosed daily by gavage over gestation day 6–15 with undiluted DEG at dosages of 0.0 (controls), 0.5, 2.5 or 10.0 ml/kg/day (equivalent to 0, 559, 2795 and 11,180 mg/kg/day). Controls received 10 ml/kg/day of deionized water. All females were examined daily for any clinical signs of toxicity. They were weighed on gestation days 0, 6, 9, 12, 15 and 18, and body weight changes calculated for the inter-weighing periods. Food and water consumption was

measured at sequential 3-day intervals over gestation days 0–18. All surviving females were sacrificed on gestation day 18 by CO_2 asphyxiation.

Midline thoracolaparotomy was performed, and the gravid uterus, ovaries, cervix, vagina, and abdominal and thoracic cavities examined grossly. Corpora lutea were counted. Gravid uterine, liver, and kidney weights were recorded. The uterus was dissected longitudinally and all live and dead foetuses and resorption sites were recorded. Live foetuses were weighed, sexed, and examined for any external malformations or variations. All live foetuses in each litter were examined for thoracic and abdominal visceral abnormalities. One-half of the foetuses from each litter were decapitated and heads fixed in Bouin's solution for examination of craniofacial structures by sectioning. All foetuses (50% intact, 50% decapitated) were eviscerated, fixed in ethanol, processed for skeletal staining with alizarin red S, and examined for skeletal malformations and variations.

6 of 30 females dosed with 11,180 mg/kg bw/day died from gestation days 7–10, that is after 1–5 days of dosing with undiluted DEG. There were no mortalities in the mid and low dosage groups. Necropsy findings of these animals included colour changes in the glandular and non-glandular portions of the stomach and colour changes in the lungs. The cause of death is not known. Clinical signs were only seen at 11,180 mg/kg bw/day and included hypoactivity, prostration, laboured and slowed breathing, and cold extremities. Body weights and body weight changes were comparable across all groups. Food consumption was unaffected. For water consumption, statistically significant increases were measured at 11,180 mg/kg bw/day, and for 2795 mg/kg bw/day. There were no treatment related necropsy findings after sacrifice on gestation day 18, and no statistically significant effects on gravid uterine, liver or kidney weights. The overall pregnancy rate was equivalent across all dosage groups, ranging 86.7–100%. There were no effects on number of corpora lutea, nor on total, viable and non-viable implantations. Foetal sex ratios was unaffected. For all foetuses and female foetuses body weights were significantly reduced at 11,180 mg/kg bw/day, male foetal weights at the high dose were reduced but not with statistical significance. There were no statistically significant increases in the incidences of malformations or variations by category (external, visceral or skeletal) or in the incidences of individual malformations or variations.

The authors concluded that under the conditions of these studies, the no-observed-effect-level (NOEL) for DEG given by gavage over gestation days 6–15 was 559 mg/kg bw/day for maternal toxicity, and 2795 mg/kg bw/day for developmental toxicity (foetotoxicity). There were no indications of embryotoxicity or teratogenic effects in mice at any dosage.

Ref.: 11

Rats

Guideline:	/
Species/strain:	Virgin male and virgin female Crl: CD (ICR) BR albino rats
Group size:	25 timed pregnant per dose
Test substance:	Diethylene glycol
Batch:	TFJ-44408 PL26032
Purity:	99.87%, [ethylene glycol 0.02%, triethylene glycol 0.11%]
Dose level:	0.0 (controls) 1.0, 4.0 or 8 ml/kg bw/day (equivalent to 0, 1118, 4472, and 8944 mg/kg bw/day
Route:	Oral, gavage
Observation:	21 gestation days
GLP:	/

Timed-pregnant CD rats, 25 per group, were dosed daily by gavage over GD 6–15 with undiluted DEG at dosages of 0.0, 1.0, 4.0 or 8.0 ml/kg bw/day (equivalent to 0, 1118, 4472 and 8944 mg/kg bw/day). Controls received deionized water at 8.0 ml/kg bw/day. Surviving

females were sacrificed on GD 21 by CO_2 asphyxiation. Procedures for maternal examinations were as for the mice, but with the additions that body weights were also determined on GD 21 and food and water were measured over GD 18–21. Foetal examinations were as described above for mice.

3 females of the 8944 mg/kg bw/day group died on GD 11. Signs before death included cold extremities, slow or audible breathing, and hypoactivity. Signs were not seen in animals of the lower dosage groups. Body weights were statistically equivalent across the control and DEG groups. Body weight gains were significantly decreased in the 8944 mg/kg/day group ($p < 0.01$). Food consumption was decreased and water consumption increased for the 4472 and 8944 mg/kg bw/day. At necropsy the kidneys of two of the three animals of the 8944 mg/kg bw/day group that died were enlarged. Histology for all kidneys from all 3 rats showed moderate to severe tubular vacuolization and proteinosis. In the rats from this group that survived to scheduled sacrifice on GD 21, renal histology showed tubular basophilia and interstitial nephritis, indicating renal tubular repair. Kidneys from the other groups were histologically normal. At scheduled sacrifice, the 8944 mg/kg bw/day group had increased relative liver weight and increased absolute and relative weights of the kidneys. Pregnancy rates were equivalent across the control and DEG groups, ranging 92–100%. No differences were seen between the controls and DEG groups with respect to corpora lutea, and total, viable and non-viable implants. Foetal sex ratio was unaffected. Foetal body weights were significantly reduced at 8944 mg/kg bw/day for both males and females. There were no significant differences in the incidence of total malformations or by category or individual malformations. Total variations or by category did not show any treatment-related increases. However, the incidence of the following individual skeletal variations were increased in the 8944 mg/kg bw/day group; poorly ossified interparietal, poorly ossified thoracic centre #10 and #13, and bilobed thoracic centre #10. Also, split anterior arch of the atlas was increased in this high dosage group, but not with statistical significance. At 4472 mg/kg bw/day split anterior arch of the atlas and bilobed thoracic ossification centre #10 were increased with statistical significance.

The authors concluded that under the conditions of these studies, the no-observed-effect-level (NOEL) for DEG given by gavage over GD 6–15 was 1118 mg/kg bw/day for maternal toxicity, and 1118 mg/kg bw/day for developmental toxicity (foetotoxicity). There were no indications of embryotoxicity or teratogenic effects in rats at any dosage.

Ref.: 11

Rabbits

Teratogenicity was evaluated in pregnant Dutch rabbits (8/group) exposed by inhalation to diethylene glycol at nominal concentrations of 0, 100, 250 or 450 ppm on gestation days (GD) 6-18. All surviving rabbits were sacrificed on GD 21. There were significant differences observed between treated and control animals in the following: decreased body weight and food consumption (high-dose group), increased mean percentage pre-implantation losses and litters with any pre-implantation loss (100 and 450 ppm), mean number of intra-uterine deaths (450 ppm), and decreased mean foetal and gravid uterine weights (all treated groups). There were no significant differences observed between treated and control animals in the following: maternal mortality, haematology values, organ weights, and macroscopic observations, post-implantation loss, and mean number of live foetuses. One high-dose group rabbit was found to have marked ataxia, loss of withdrawal reflex, and slight head tremors; this rabbit was sacrificed and found to have undergone 100% post-implantation losses.

Ref.: 12

3.3.9. Toxicokinetics

3.3.9.1. Toxicokinetics *in vitro*

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3.3.9.2. Toxicokinetics *in vivo*

Oral doses of DEG are rapidly and almost completely absorbed in rats, with 96% absorption of a 1 ml/kg bw/day dose within 30-120 minutes. Tissue and organ distribution from blood occurred rapidly in the rat following oral exposures and occurred in the following sequence: kidneys, brain, spleen, liver, muscle and fat.

The metabolic pathway in rats has been demonstrated to involve oxidation by alcohol dehydrogenase followed by oxidation to 2-hydroxyacetic acid (HEAA) by aldehyde dehydrogenase.

DEG is excreted unchanged by kidney at a variable proportion (40-70 %). After intragastric administration to rats, 10.7% of the dose was excreted as HEAA.

Elimination half-life of 3.6 hours was calculated following multiple dosing, which followed a first order kinetic pattern.

The mechanism of toxicity is unknown. It has been suggested that hygroscopic swelling of parenchymatous cells causes obstruction of the kidney tubule lumen. Although the exact mechanism of DEG neurotoxicity has not been described, it seems that HEAA may produce this kind of toxicity. Hepatotoxicity may be produced by accumulation of this metabolite inside the cells, producing cellular lysis of the hepatic cells and kidney tubules.

3.3.10. Photo-induced toxicity

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3.3.11. Human data

DEG is toxic primarily to the kidney and nervous system and can produce a wide variety of signs and symptoms after consumption. Patients typically develop acute renal failure (ARF) and may present with metabolic acidosis. In several medication associated DEG mass poisonings, the clinical picture included ARF and neurologic symptoms, including encephalopathy, coma, and death. The lack of information on the short- and long-term effects of DEG exposure is matched by a scarcity of information on the manner in which DEG is metabolized and eliminated after ingestion and how it causes its specific end-organ effects in humans.

The exact pathophysiology of DEG-induced illness is still unclear. Limited evidence suggests that HEAA, the principal metabolite of DEG, is toxic, but there are indications that it is not the only toxic agent. More work remains to be done on elucidating the pathophysiology of DEG-induced illness, as well as in clarifying short- and long-term outcomes of DEG-poisoned patients.

Ref.: 13

The initial symptoms of DEG intoxication are nausea, headache and vomiting. With continued use, severe abdominal pain, polyuria followed by oliguria, anuria and renal failure

may appear. Hepatotoxicity is common. In the Central Nervous System (CNS), DEG may produce drowsiness, coma, demyelinating lesions of the central and peripheral nervous systems, as well as tremor and seizures. DEG also can cause respiratory arrest and pulmonary oedema.

The toxicity of DEG had not been documented prior to the first instance of mass poisoning. The first incident of mass poisoning by DEG, known as the Massengill incident, uncovered similar symptoms of toxicity between ethylene glycol and DEG. The Massengill incident occurred in 1937 when a sulfanilamide drug was prepared with DEG. After consumption of this drug, 105 adults and children died. After this initial incident where DEG was intentially used as the diluent in a pharmaceutical product, several other instances have occurred, primarily in developing countries, where DEG was mistakenly used as a diluent instead of more common diluents such as propylene glycol and glycerol. Historical mass poisonings by DEG is presented in Table 1.

Ref.: 14

The mass poisonings will be briefly discussed below.

Table 1: *Historical mass poisonings by DEG* (from ref.: 14 with some modifications)

Year	Place	Vehicle	Expected Diluent	Number died	Ref.
1937	USA	Sulfur drug	DEG	105	15,16
1969	South Africa	Sedative elixirs	Propylene glycol	7	17
1985	Spain	Topical cream (silver sulfadiazine)	NA[c]	5	18
1986	India	Glycerol	Glycerol	14 or 21	19
1990	Nigeria	Paracetamol syrup	Propylene glycol	47	20
1990-1992	Bangladesh	Paracetamol syrup	Glycerol/ propylene glycol	236	21
1992	Argentina	Propolis (a substance produced by bees)	Glycerol	15	22,23
1995	Haiti	Paracetamol syrup	Glycerol	88	24
1998	India	Expectorant syrup	Glycerol	36	25
2006	Panama	Antihistamine/ expectoratans	Glycerol	51	13

[c] NA = not stated

The Elixir Sulfanilamide disaster of 1937 was one of the most consequential mass poisonings of the 20th century. This tragedy occurred shortly after the introduction of sulfanilamide, the first sulfa antimicrobial drug, when DEG was used as the diluent in the formulation of a liquid preparation of sulfanilamide known as Elixir Sulfanilamide. The Elixir contained 72% DEG. 353 patients received Elixir Sulfanilamide during a 4-week period in the fall of 1937. There were 105 deaths (34 children and 71 adults) and 248 survivors. The drug was administered on the direction of a physician in 100 of the 105 patients who died. Reasons for use included gonorrhea, sore throat, ear infections, soft-tissue infections and syphilis. The directions stated "Begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-hour to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery". The mean fatal dose of DEG was 38 g in children and 71 g in adults. Survival time from the first dose was 9.4 days (range 2 to 22 days).

'The earliest clinical symptoms were nausea and vomiting. Later symptoms included manifestations of renal failure such as polyuria, anuria, flank pain, coma, and, in some patients seizures. *Post-mortem* examinations were most remarkable for "hydropic tubular nephrosis", a finding that would now be called vacuolar nephropathy. Liver examination showed central degeneration.

Ref.: 15, 16

In 1969, an epidemic of fatal renal failure occurred among seven children in Cape Town, South Africa. As therapy for fever, sedatives formulated with DEG instead of propylene glycol were given to each child. Shortly after the children received the medication, vomiting, diarrhoea, and dehydration developed. Anuria, acidotic breathing, hepatomegaly, and unresponsiveness ensued. *Post-mortem* examination showed extensive tubular necrosis of the kidney and centrilobular hydropic degeneration of the liver.

Ref.: 17

During the first 3 months of 1985, 5 patients with burns developed anuric acute renal failure after submission to a hospital in Spain with second- and third-degree burns involving 7 – 62% of the body surface. Between the 3rd and 6th day of topical treatment, the patients developed oligoanurea. All 5 patients died. The kidney findings on autopsy in the last patient showed tubular dilation with ballooning, flattening of the tubular epithelia, and interstitial oedema with little interstitial infiltrate. Calcium oxalate crystals were not present.

Just before these incidents, a new 1% silver sulfadiazine formulation was introduced. Analyses of the silver sulfadiazine medication used showed that it contained DEG in an amount of 6.2 to 7.1 g/kg of substance (0.62 – 0.71%). The presence of sodium lauryl sulphate in the formulation may have enhanced the dermal absorption of DEG.

Ref.: 18

In another DEG-mediated catastrophe, 14 (Ref. 14 divergently stated 21 deaths) unexpected deaths from renal failure occurred at a hospital in Bombay, India, in 1986. The patients (ages ranged from 10 to 76) had been hospitalized for various conditions, including brain tumours, head injuries, glaucoma, cataract, iridocyclitis and cerebral vascular accidents. All affected patients were supposed to receive medicinal glycerol for its osmotic diuretic effect. Instead, they each received the less costly industrial glycerol, which contained 18.5% DEG. Vomiting, diarrhoea, gastrointestinal bleeding, abdominal pain, guarding, rigidity, and distension set in within four to five days of the administration of the toxic glycerin. Over a further two to three days oliguria, anuria, acidosis, and instability of blood pressure followed. At necropsy acute, extensive cortical necrosis was seen in the kidneys. The liver showed centrilobular necrosis. Extensive haemorrhages were seen in the adrenal medullae. Rats and rabbits fed the toxic glycerol also showed extensive renal damage.

Ref.: 19

During the summer months of 1990, approximately 47 children ranging in age from 6 months to 23 months died unexpectedly from renal failure in Nigeria. All children had fever prior to developing acute renal failure. Attending physicians quickly identified a paracetamol syrup that they had all previously received for treatment of upper respiratory tract infections or malaria. An investigation showed that local chemists had substituted DEG for propylene glycol in the paracetamol preparation.

Ref.: 20

A dramatic increase in the number of patients with unexplained renal failure was admitted in 1990 to Dhaka Shishu Hospital, the major children's hospital in the capital of Bangladesh. Beginning in November 1990 possible causes for this increase were sought. From 1 January 1990 to 1 December 1992, 429 patients with acute renal failure had been admitted to the renal unit. Paracetamol elixir was identified as the medicine most commonly taken before admission by patients developing unexplained renal failure. This investigation strongly implicated DEG in paracetamol elixirs as the cause of the epidemic. The government of Bangladesh banned the sale of paracetamol elixirs in December 1992. It was estimated that 236 children died from the paracetamol contaminated with DEG in the period 1990 – 1992.

Ref.: 21

Fifteen mortal intoxications due to the ingestion of a Propolis syrup contaminated with DEG were studied in Argentina in 1992. Propolis is a resin elaborated by bees, used to build their beehives, with antimicrobial, anti-inflammatory and antioxidant properties. The analysis of the samples demonstrated that the Propolis syrup contained 55% DEG (w/v), propylene glycol (PEG), solid remainders and water. Patients were adults, with age between 50 and 93 years old. The average lethal dose estimated was between 14-175 mg/kg bw/day. Taking into account the contributed information by the patients or their family, the ingested dose of the syrup was estimated between 5-20 ml. The report does not state the time period in which the patient took this syrup.

Ref.: 22, 23

Comment
The average lethal dose given probably represents the daily dose. This dose is 10 – 100 times lower than that reported in other mass poisonings, and does not appear reliable. Reference 23 contains several errors in that the unit for the amount of DEG is given as "mg" in the paper, while it should be "g". The errors are corrected above.

Another report exposes the study of 98 cases of paediatric patients of Haiti, with ages between one month and thirteen years old that had ingested paracetamol syrup contaminated with DEG. 88 of the 98 patients died. Thirty six medication packages coming from the patients were analyzed. The presence of DEG was found, with a composition of 14.4% of DEG (range 1.2-19.6%). The accumulated maximum dose of DEG was estimated in 32 of the children. This value was 1.34 ml/kg bw/day (1.6 g/kg bw/day) (range 0.22-4.42 ml/kg bw/day; 260-5200 mg/kg bw/day). Twelve of these children (37.5%) ingested an estimated accumulated maximum dose less than 1 ml/kg bw/day. The average time between the first dose and the initiation of oliguria or anuria was 6 days (range 1-12 days).

Ref.: 24

Comment
The study from Haiti will be described in more details in Section 3.3.12.

A second episode of poisoning occurred in 1998 in India as a result of children ingesting DEG. A total of 36 children with unexplained acute renal failure were admitted to two hospitals in Delhi between 1 April and 9 June 1998. Most of the children (26/36) were from the Gurgaon district in Haryana or had visited Gurgaon town for treatment of a minor illness. Acute renal failure developed after an episode of acute febrile illness with or without watery diarrhoea or mild respiratory symptoms for which the children had been treated with unknown medicines by private medical practitioners. On admission to hospital the children were not dehydrated. Cough expectorant manufactured by a company in Gurgaon was found to be contaminated with DEG (17.5%v/v). Thus, poisoning with DEG seems to be the cause of acute renal failure in these children.

Ref.: 25

During October of 2006, the Centers for Disease Control and Prevention (CDC) assisted the Panamanian Ministry of Health to investigate an outbreak of renal and neurologic illness. A antihistamine/expectorants elixir used to treat a chronic cough, found to contain DEG, had been used by the patients. Concentrations of DEG measured in the implicated samples collected from patient families were 8.1 ± 1% (v/v). In samples with the same lot number collected from the manufacturer, the DEG content was 7.6 ± 0.2%. Raw glycerol collected from the manufacturer contained 22.2 ± 0.8% DEG.DEG was identified as a contaminant in cough syrup formulated in Panama and distributed to more than 30,000 residents. The ingestion of this cough syrup was implicated in over 90 cases of acute renal failure, including 51 deaths.

Ref.: 13

General comment
More than 600 deaths have occurred due to DEG mass poisonings. Most of the deaths have occurred after oral intake of medication containing DEG, primarily paracetamol, however, deaths have also occurred in patients with second- and third-degree burns following dermal exposure of DEG. Among the individuals for whom the DEG dose could be estimated there was considerable overlap in the range of doses ingested (see section 3.3.12) by the patients that died and those that survived.

The lethal dose has only been estimated in a few studies. In the first mass poisoning in 1937 in USA, it was estimated that the average lethal daily dose was 1200 mg/kg bw/day and the survival time from the first dose was 9.4 days (range 2 to 22 days) (ref. 15, 16). In a study from Argentina in 1992, the average lethal dose estimated was between 14-175 mg/kg bw/day. The best estimate is probably from the Haiti mass poisoning in 1995. Among 32 patients for whom a maximum possible ingested dose could be estimated, the median estimated DEG dose consumed was 1600 mg/kg bw/day (range 260-5200 mg/kg bw/day); 12 children (37.5%) consumed an estimated maximum DEG dose less than 1.0 ml/kg (1200 mg/kg/day). The median time from the first dose to onset of oliguria or anuria was 6 days (range, 1-12 days).

Following detection of DEG-containing toothpastes on the European market, several countries have performed national risk assessments.

The French authority state that "risks of severe and potentially fatal poisoning have been reported at doses generally in excess of 500 mg/kg, with a median of over 1 000 mg/kg". "In applying a safety factor of 10, a median can be set for the dose likely to produce toxic effects following acute oral exposure of close to 100 mg/kg, and the threshold below which the appearance of effects is improbable, even among the most sensitive individuals, can be set at 20 mg/kg". The acute TRV adopted was 20 mg/kg bw/day in young children. As described in section 3.3.5.3. The French authority considers a TRV of 2 mg/kg bw/day for repeated toxicity.

The German authority (ref. 26) points out that lethal poisoning in human may occur at 1000 mg/kg bw/day. Moreover, at doses of 50 – 80 mg/kg bw/day in rats (ref. 27), the amount of oxalic acid in urine is increased. It is noted that in humans, oxalic acid is not increased, but that the hygroscopic swelling of the parenchymatous cells of the kidney tubule lumen is of concern and that the rat study in connection with a safety factor may be used. A daily dose of more than 0.5 mg/kg bw/day was considered unsafe. This value is also in agreement with accepted TDI in the EU.

As stated in section 3.3.5, the SCCP considers that for safety assessment based on experimental animal data a NOAEL of 50 mg/kg bw/day (calcium oxalate crystals in rat bladder) may be used. This figure is in agreement with the German authority view, which was also based on animal data. However, since the repeated dose animal studies are old and of unknown quality, human data should have precedence over the animal data.

As pointed out above, the best estimate for toxic effects resulting in death is probably the median estimated DEG dose of 1600 mg/kg bw/day from the Haiti poisoning (ref. 24). By using a safety factor of 10, the intraspecies variation observed (260 – 5200 mg/kg bw/day) is covered. The median estimated DEG dose from Haiti is in agreement with the calculated dose (1200 mg/kg bw/day) from the Elixir Sulfanilamide disaster in USA in 1937.

3.3.12. Special investigations

Altogether, 109 cases of acute renal failure among children were identified in the 1995 mass poisoning in Haiti. 87 were confirmed and 22 were possible cases. The clinical syndrome included renal failure, hepatitis, pancreatitis, central nervous system impairment, coma, and death. Of 87 patients with follow-up information who remained in Haiti for treatment, 85 (98%) died in Haiti; 3 (27%) of 11 patients transported to the United States for intensive care unit management died before hospital discharge. A locally manufactured paracetamol syrup was highly associated with disease (odds ratio, 52.7; 95% confidence interval, 15.2-197.2).

A detailed medication history or bottle of medication was available for 82 of 109 affected children. A bottle of the paracetamol syrup was collected from 50 of these, and an additional 31 had exposure documented by history. Only 1 child had no history of exposure to either medication. Among 54 children for whom the timing of paracetamol syrup consumption was clearly given, the median time from the first dose to onset of oliguria or anuria was 6 days (range 1-12 days). Of 7 children who had a definite history of stopping the medication before the onset of oliguria or anuria, the median interval between stopping and noting a change in urinary frequency was 4 days (range, 2-8 days). Although other medications manufactured by the same company were also contaminated with DEG, only 1 patient consumed any other contaminated medication. The medication contained only 1.2% DEG, and this patient also consumed the paracetamol syrup with a DEG concentration of 17.2%. Among control subjects, only 2 consumed any medications contaminated with DEG. An 8-month old control subject consumed an estimated DEG dose of 0.4ml/kg in the form of paracetamol drops contaminated with 5% DEG, and an 11-month-old control subject consumed an iron supplement produced by the manufacturer that was contaminated with an unknown proportion of DEG.

Samples of the paracetamol syrup were analyzed to determine the toxic substance contained therein. DEG was identified in bottles from patients, unopened bottles purchased in pharmacies, and retained quality control samples from the manufacturer. Among 36 contaminated patient bottles tested, the median DEG concentration was 14.4% (range, 1.2%-19.6%). Among 32 patients for whom a maximum possible ingested dose could be estimated, the median estimated DEG dose consumed was 1.34 ml/kg (1600 mg/kg) (range, 0.22-4.42 ml/kg; 260-5200 mg/kg); 12 children (37.5%) consumed an estimated maximum DEG dose less than 1.0 ml/kg (1200 mg/kg).

Forty-nine well children who ingested a DEG-contaminated lot of paracetamol syrup were enrolled in a prospective cohort study and followed up for a median of 87 days (range, 19-175 days) after the last dose of paracetamol syrup. If the date of last ingestion was unknown, the follow-up period began with the first clinical visit. The median age of children was 45 months (range, 1-154 months), and the median ingested DEG dose among 17 children was 0.67 ml/kg (0.05-2.48 ml/kg).

One hundred thirty-eight children from both the case-control study and the cohort group who consumed paracetamol syrup from a DEG-contaminated lot were included in an analysis of risk factors for disease. The mean age of children who became ill was 39.5 months compared with 52.1 months among children who did not (P=.05). Cases were more likely to have taken the paracetamol syrup for symptoms of diarrhoea (OR, 4.3; 95% CI, 1.7-10.9) or vomiting (OR, 8.8; 95%CI, 3.7-21.8) than were children who did not develop symptoms of DEG toxicity. 49 children survived through the follow-up period, and none developed overt signs or symptoms of DEG toxicity; however, numerous children had laboratory evidence of sub-clinical toxic effects. Among the individuals for whom we could estimate the DEG dose ingested per kilogram, children who became ill consumed a mean

dose of 1.34 ml/kg, compared with 0.84 ml/kg among those who did not (*P*=.04); however, there was considerable overlap in the range of doses ingested (see Fig 1).

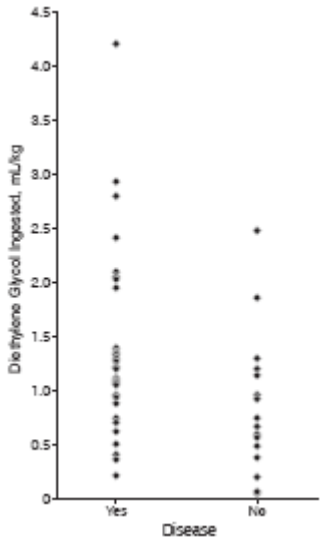

Figure 1: Maximum concentration of DEG ingested among the children who became ill (Yes) and among those who did not became ill (No) after exposure to a contaminated paracetamol syrup (taken from ref. 24).

A trace-back investigation at the manufacturer revealed that glycerol, used in the formulation of these syrups, was contaminated with 24% DEG. The glycerol had been imported to Haiti through distributors in Europe from a manufacturer in China. It is unknown how and at which point the contamination occurred or if other countries received DEG-contaminated glycerol.

Although 17 liquid medications were likely contaminated with DEG, only DEG-contaminated paracetamol syrup was epidemiologically associated with illness. There may be several reasons for this finding. Paracetamol may provide an additive or potentiating effect for DEG toxicity since both are toxic to the liver and may alter the metabolism of DEG.

The mechanism of DEG toxicity in humans is not well characterized, and minimum toxic dose ranges have not been well established. A DEG dose of 1ml/kg has been suggested as the minimum toxic dose; however, there is little evidence to support this. This study documented that toxic doses are often less than 1 ml/kg; therefore, clinical outcome should not be predicted based on this cut off value. The intervals from the first DEG exposure and the last DEG exposure to onset of illness indicate that, if disease is going to occur, it will present within a short time after exposure.

Ref.: 24

3.3.13. Safety evaluation

More than 600 deaths have occurred due to DEG mass poisonings. Although most of the deaths have occurred after oral intake, deaths are also reported after dermal exposure. Overall, the data available reports mainly on lethal events. Reliable data on non-lethal repeated dose toxicity and dermal absorption, which would allow assessment of the safety of use in cosmetic products, is not available. Based on this, DEG should not be used intentionally in cosmetic products.

COLIPA stated in a letter of 5 October 2007 that they has been informed by its member companies that DEG is not intentionally added as an ingredient to oral care products. However, DEG can be present as an impurity in glycerol and polyethylene glycols, which are common ingredients in oral care products. Small amounts of DEG may therefore be present in the final product via the use of these ingredients resulting in maximum levels of DEG in these products of 0.1%.

For safety evaluation of the presence of DEG as impurity in cosmetic products, the median estimated DEG dose for lethal effect of 1600 mg/kg bw/day will be used as starting point.

The following safety factors will be used:

10 for intra-species variation
10 for converting acute dose to chronic dose (see ref. 28-30).
10 for the seriousness (death) of the effect.

Thus, if the results from the mass poisonings are used, a dose of **1.6 mg/kg bw/day** should be safe.

Based on animal data, the TDI in the EU has been determined to be 0.5 mg/kg bw/day. This is in agreement with the value considered safe in the risk assessment by the German authorities.

Following the worst-case consideration that all cosmetic products (18 g daily, according to SCCP Notes of guidance) contain 0.1% DEG and that the dermal absorbance is 100%, the systemic dose will be ([18000 x 0.001]/60) **0.3 mg/kg bw/day**.

If all oral hygiene products (3.48 g daily, according to SCCP Notes of guidance) contain 0.1% DEG, the systemic dose will be ([3480 x 0.001]/60) **0.06 mg/kg bw/day.**

Based on the above calculations, the total systemic dose (the sum of dermal and oral exposure) when DEG is present as an impurity at maximum 0.1% will be less than ~~**0.4**~~ **0.3 mg/kg bw/day.**

Thus, a maximum concentration of up to 0.1% DEG from impurities in ingredients like glycerine and polyethylene glycols in the finished cosmetic products is considered to be safe, when compared to safe limits derived from both human and animal data.

3.3.14. Discussion

Physico-chemical specifications
DEG is a colourless syrupy liquid, practically odourless with a sharply sweetish taste. It is highly hygroscopic. No information is available concerning stability.

General toxicity
The data on repeated toxicity of DEG are old and it can not be excluded that the presence of ethylene glycol as impurity in the DEG may have influenced the results. SCCP consider that a NOAEL of 50 mg/kg bw/day based on formation of calcium oxalate crystals in the rat bladder could be used.

DEG at 3.5% was a reproductive toxicant in Swiss mice, based on reductions in litters/pair, and in mean litter size. In F_0 mice, this was unaccompanied by body weight loss, while in F_1 mice, there was reduced body weight in the absence of a fertility effect. No effects were observed at 0.35 % (612 mg/kg bw/day).

The NOEL for DEG given by gavage over gestation days 6–15 was 559 mg/kg/day with the mouse and 1118 mg/kg bw/day for rats for maternal toxicity, and 2795 mg/kg/day with

mice and 1118 mg/kg bw/day for rats for developmental toxicity (foetotoxicity). There were no indications of embryotoxicity or teratogenic effects at any dosage.

More than 600 deaths have occurred due to DEG mass poisonings. DEG is toxic primarily to the kidney and nervous system and can produce a wide variety of signs and symptoms after consumption. Patients typically develop acute renal failure (ARF) and may present with metabolic acidosis. After the initial incident where DEG was intentionally used as the diluent in a pharmaceutical product, several other instances have occurred, primarily in developing countries, where DEG was mistakenly used as a diluent instead of more common diluents such as propylene glycol and glycerol.

Most of the deaths have occurred after oral intake of medications, primarily paracetamol, containing DEG. However, deaths have also occurred in patients with second- and third-degree burns following dermal exposure of DEG. The lethal dose has only been estimated in a few studies. The best estimate for toxic effects resulting in death is probably the median estimated DEG dose of 1600 mg/kg bw/day from the Haiti poisoning. This dose is in agreement with the calculated dose (1200 mg/kg bw/day) from the Elixir Sulfanilamide disaster in USA in 1937. By using a safety factor of 1000 (10 for intraspecies variation, 10 for converting acute dose to chronic dose and 10 for converting LOAEL to NOAEL and considering the seriousness (death) of the effect). Thus, if the results from the mass poisonings are used, a dose of **1.6 mg/kg bw/day** should be safe. Based on animal data, the TDI in the EU has been determined to be 0.5 mg/kg bw/day. This is in agreement with the value considered safe in the risk assessment by the German authorities. Thus, a maximum concentration of up to 0.1% DEG from impurities in ingredients like glycerine and polyethylene glycols in the finished cosmetic products is considered to be safe, when compared to safe limits derived from both human and animal data.

Toxicokinetics
The metabolic pathway in rats has been demonstrated to involve oxidation by alcohol dehydrogenase followed by oxidation to 2-hydroxyacetic acid (HEAA) by aldehyde dehydrogenase.

The mechanism of toxicity is unknown. It has been suggested that hygroscopic swelling of parenchymatous cells causes obstruction of the kidney tubule lumen. Although the exact mechanism of DEG neurotoxicity has not been described, it seems that HEAA may produce this kind of toxicity. Hepatotoxicity may be produced by accumulation of this metabolite inside the cells, producing cellular lysis of the hepatic cells and kidney tubules.

Irritation, sensitisation
DEG is not considered to be a skin or mucous membrane irritant.

Dermal absorption
Dermal absorption has been reported to be about 10%. However, since no information about how the dermal absorption was estimated is available, SCCP will use 100 % dermal absorption in the risk considerations.

Mutagenicity
DEG was not mutagenic in the Salmonella assay. The results of *in vitro assays* of DEG for chromosomal aberrations and in sister chromatid exchange assays have also been uniformly negative.

Carcinogenicity
Bladder tumours, mostly benign, occurred at 1,500 and 3,000 mg/kg/day in male rats treated with DEG for two years. These tumours were associated with irritation from bladder stones which occurred at those doses. Other results indicate that DEG substantially free of ethylene glycol does not cause bladder stones.

4. CONCLUSION

SCCP is of the opinion that diethylene glycol (DEG) should not be used as an ingredient in cosmetic products including oral care products. This opinion is based on the fact that more than 600 deaths have occurred due to DEG mass poisonings. Although most of the deaths have occurred after oral intake, deaths are also reported after dermal exposure. In addition, reliable data in line with present guideline requirements on non-lethal repeated dose toxicity and dermal absorption, which would allow assessment of the safety of use in cosmetic products, is not available.

SCCP is of the opinion that a maximum concentration of up to 0.1% DEG from impurities in ingredients like glycerine and polyethylene glycols in the finished cosmetic products can be considered to be safe.

5. MINORITY OPINION

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