Danish Ministry of the Environment
Environmental Protection Agency

Evaluation of health hazards by exposure to

Propylene glycol 1-ethyl ether and its acetate (2PG1EE and 2PG1EEA)

and proposal of a health-based quality criterion for ambient air

Environmental Project No. 1498, 2013

Title:

Evaluation of health hazards by exposure to Propylene glycol 1-ethyl ether and its acetate (2PG1EE and 2PG1EEA) and proposal of a health-based quality criterion for ambient air.

Editing:

Elsa Nielsen, Ole Ladefoged
Division of Toxicology and Risk Assessment.
National Food Institute, Technical University of Denmark.

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Content

Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to Propylene glycol 1-ethyl ether and its acetate (2PG1EE and 2PG1EEA), and a proposal of a health based quality criterion for ambient air. This resulted in 2006 in the present report, which was prepared by Elsa Nielsen and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Working Environment Authority,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
The Danish Environmental Protection Agency

The Danish Environmental Protection Agency
Copenhagen, September 2013.

1 General description

Commercial propylene glycol mono ethyl ether (PGEE) is a mixture of 2-propylene glycol 1-ethyl ether (2PG1EE, α-isomer) (CAS-no.: 1569-02-4) and 1-propylene glycol 2-ethyl ether (1PG2EE, β-isomer) (CAS-no.: 19089-47-5). Usually, the β-isomer constitutes less than 10% of commercial PGEE (ECETOC 1995a). The CAS-no. 52125-53-8 covers PGEE where the alkoxy position is unspecified. 1PG2EE is of little or no commercial importance (Gingell et al. 1994).

Commercial propylene glycol mono ethyl ether acetate (PGEEA) is a mixture of 2-propylene glycol 1-ethyl ether acetate (2PG1EEA, α-isomer) (CAS-no.: 54839-24-6) and 1-propylene glycol 2-ethyl ether acetate (1PG2EEA, β-isomer) (CAS-no.: 57350-24-0). Usually, the β-isomer constitutes less than 10% of commercial PGEEA (ECETOC 1995b). The CAS-no. 98516-30-4 covers PGEEA where the alkoxy position is unspecified.

In this report, the α-isomer (2PG1EE) of PGEE is evaluated. As propylene glycol ether acetates generally are rapidly metabolised to the parent propylene glycol ethers following absorption and as the toxicity of the acetates are expected to be very similar to that of parent ethers, 2PG1EE and 2PG1EEA will be evaluated concurrently in this document.

No data regarding the toxicity of 1PG2EE and 1PG2EEA have been found.

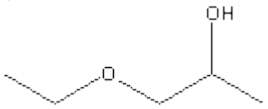
1.1 Identity

Substance:
1) 2-Propylene glycol 1-ethyl ether
2) 2-Propylene glycol 1-ethyl ether acetate
3) 1-Propylene glycol 2-ethyl ether
4) 1-Propylene glycol 2-ethyl ether acetate

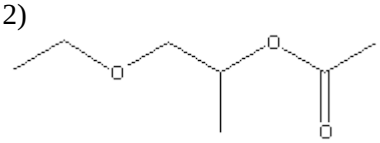
Molecular formula:
1) $C_5H_{12}O_2$
2) $C_7H_{14}O_3$
3) $C_5H_{12}O_2$
4) $C_7H_{14}O_3$

Structural formula:

1)



2)



3) C_2H_5-O-CH_2-CH_2-CH_2OH

4) C_2H_5-O-CH_2-CH_2-CH_2O-($COCH_3$)

Molecular weight:	1) 104.15 2) 146.19 3) 104.15 4) 146.19
CAS-no.:	1) 1569-02-4 2) 54839-24-6 3) 19089-47-5 4) 57350-24-0
Synonyms:	1) 1-Ethoxy-2-propanol 2PG1EE Propasol Solvent E 2) 1-Ethoxy-2-propyl acetate 2PG1EEA 3) 2-Ethoxy-1-propanol 1PG2EE 4) 2-Ethoxy-1-propyl acetate 1PG2EEA

1.2 Physical / chemical properties

Description:	1) 2PG1EE is a liquid. 2) 2PG1EEA is a liquid.
Purity:	-
Melting point:	1) -90 °C 2) -89 °C
Boiling point:	1) 132 °C 2) 158 °C
Density:	1) 0.896 g/ml (at 20°C) 2) 0.941 g/ml (at 20°C)
Vapour pressure:	1) 7.5 mmHg (1000 Pa) at 20°C 8.2 mmHg (1093 Pa) at 25°C 2) 1.7 mmHg (227 Pa) at 20°C 1.5 mmHg (203 Pa) at 25°C
Concentration of saturated vapours:	1) 9870 ppm (42700 mg/m^3) (calculated) 2) 2235 ppm (13600 mg/m^3) (calculated) (at 25°C and 760 mmHg)
Vapour density:	1) 3.59 (air = 1) 2) -
Conversion factor:	1) 1 ppm = 4.33 mg/m^3 20°C 1 mg/m^3 = 0.231 ppm 1 atm

	2) 1 ppm = 6.08 mg/m^3 20°C 1 mg/m^3 = 0.164 ppm 1 atm
Flash point:	1) 43 °C (closed cup), 54.4 °C (open cup) 2) 53 °C (closed cup)
Flammable limits:	1) 1.3-12 (v/v% in air) 2) -
Auto ignition temp.:	1) 255 °C 2) 325 °C
Solubility:	1) Water: completely soluble. 2) Water: 95 g/l (at 20 °C).
$logP_{octanol/water}$:	1) - 2) 0.76
Henry's constant:	-
pK_a-value:	-
Stability:	-
Incompatibilities:	-
Odour threshold, air:	1) - 2) The odour threshold of 2PG1EEA has been measured (odour-panel) to be 0.0089 mg/m^3 (dk-Teknik 1992).
Odour threshold, water:	-
Taste threshold, water:	-
References:	IUCLID (2000a,b), ECETOC (1995a,b), Gingell et al. (1994).

1.3 Production and use

No specific data regarding production and use of 2PG1EE and 2PG1EEA have been found.

The ethers of mono-, di-, tri-, and polypropylene glycol are generally prepared commercially by reacting propylene oxide with the alcohol of choice in the presence of a catalyst. They may also be prepared by direct alkylation of the selected glycol with an appropriate alkylating agent. Preparation under commercial conditions yields products that are mixtures of the alpha and beta isomers, largely alpha. (Gingell et al. 1994).

These glycol ethers are used as solvents for surface coatings, inks, lacquers, paints, resins, dyes, agricultural chemicals, and other oils and greases. The di- and tripropylene series are also used as ingredients in hydraulic brake fluids. (Gingell et al. 1994).

1.4 Environmental occurrence

No data have been found.

1.5 Environmental fate

In activated sludge, 2PG1EE was readily biodegradable (97% after 48 hours) (BP Chemicals 1993 – quoted from IUCLID 2000a).

In industrial activated sludge, biodegradation of 2PG1EE (99.5 mg/l related to DOC (dissolved organic carbon)) reached 88% after 28 days (BP Chemicals 1985 – quoted from IUCLID 2000a).

In industrial activated sludge, biodegradation of 2PG1EEA (2 mg/l related to DOC (dissolved organic carbon)) reached 100% after 28 days (OECD Guideline 301 D "Ready biodegradability: closed bottle test") (BP Chemicals 1985 – quoted from IUCLID 2000b).

1.6 Human exposure

No data have been found.

2 Toxicokinetics

Generally, glycol ethers and their acetates are readily absorbed and distributed throughout the body following inhalation or oral administration and no substantial accumulation of the parent compound has been observed. Dermal absorption is also an important exposure route. Glycol ethers follow two main oxidative pathways of metabolism, either via alcohol dehydrogenase or the microsomal P-450 mixed function oxidase (O-demethylation or O-dealkylation). The first pathway gives rise to the formation and excretion of alkoxyacetic acids whereas the latter mainly leads to the production and exhalation of carbon dioxide via their respective glycol, which enter intermediary metabolism via the tricarboxylic acid cycle. In addition to these pathways, conjugation with sulphate, glucuronic acid or glycine has also been reported. (ECETOC 1995c).

Propylene glycol ethers with the ether bond on the primary carbon, e.g., 2PG1EE, are secondary alcohols and are primarily metabolised to carbon dioxide. The existing metabolism studies provide no indications of these substances being metabolised to alkoxy propionic acids.
Propylene glycol ethers with the ether bond on the secondary carbon, e.g., 1PG2EE, are primary alcohols and are metabolised to alkoxy propionic acids, presumably by alcohol dehydrogenase.
(ECETOC 1995c).

No specific data regarding the toxicokinetics of 2PG1EE and 2PG1EEA have been found.

2.1 Toxicological mechanisms

A number of glycol ethers and their acetates have been shown to cause haematological, immunological, testicular, and developmental toxicity; these toxic effects appear to be dependent on the formation of alkoxy acetic or alkoxy propionic acids.

Propylene glycol ethers and their acetates only show developmental toxicity if the ether bond is present on the secondary carbon atom (e.g., 1PG2ME, 1PG2EE, 1PG2EEA); this allows the primary alcohol to be oxidised to an alkoxy-propionic acid. Propylene glycol ethers with the ether bond on the primary carbon atom (e.g., 2PG1ME, 2PG1EE, 2PG1EEA) are secondary alcohols and are not metabolised to alkoxy-propionic acids; these ethers and their acetates have not shown developmental toxicity. (ECETOC 1995c).

3 Human toxicity

No data regarding effects in humans following exposure to 2PG1EE and 2PG1EEA have been found.

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

2PG1EE

No mortality occurred in rats exposed for 4 hours (whole body exposure to 3337 ppm (14500 mg/m^3) or nose-only exposure to 2232 ppm (9660 mg/m^3)). Signs of toxicity were CNS depression at both concentrations, and salivation and lachrymation at the higher concentration. All effects were reversible. (BP Chemicals 1981, 1983, 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

All of five rats exposed for 4 hours to a concentration calculated to be 10000 ppm (43300 mg/m^3) survived, but showed signs of marked irritation to the eyes and nares, and were anaesthetised by the end of the exposure period (Rowe 1948 – quoted from Gingell et al. 1994).

No evidence of effect on respiratory rate, and by implication sensory irritation, was observed in mice exposed nose-only to vapour concentrations of 2800 to 7200 mg/m^3 (BP Chemicals 1983, 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

A mouse, a guinea pig and a rabbit tolerated up to 7000 ppm (30300 mg/m^3) for one hour without effect other than irritation of the eyes and respiratory tract. Exposure for 2 hours caused more severe irritation and a rabbit showed signs of kidney injury, transient albuminuria and red cells in the urine. (Gross 1938 – quoted from Gingell et al. 1994).

2PG1EEA

No mortality was observed among rats (5 males and females) exposed for 4 hours to 6990 mg/m^3 (the highest achievable droplet free vapour concentration). The only effects observed were indicative of irritation of the eyes and nose. (BP Chemicals 1985 – quoted from IUCLID 2000b and ECETOC 1995b).

4.1.2 Oral intake

2PG1EE

Rats (5 males and females per group) received PGEE as single oral doses up to 5 ml/kg b.w. All rats survived for 14 days. Signs of toxicity were indicative of mild CNS depression between one and 6 hours after treatment; these effects were fully reversible. Oral doses of 2 ml/kg b.w. were without effect. The LD_{50}-value was greater than 5000 mg/kg b.w. (BP Chemicals 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EE was fed to rats as a 50% aqueous solution; the LD_{50}-value was found to be 7110 mg/kg b.w. (Smyth et al. 1941 – quoted from Gingell et al. 1994).

An oral LD_{50}-value of more than 5000 mg/kg b.w. has been reported for rats for a commercial product. Marked narcosis and some kidney injury were observed from large doses. No further details are given. (Rowe 1947 - quoted from Gingell et al. 1994).

2PG1EEA

The oral LD_{50}-value was greater than 5000 mg/kg b.w. for rats (OECD Guideline 401). Signs of toxicity were non-specific including lethargy, salivation and pallor of the extremities. All animals were reported as normal by day 4. (BP Chemicals 1985 – quoted from IUCLID 2000b and ECETOC 1995b).

4.1.3 Dermal contact

2PG1EE

When the test material was topically applied to the skin of rabbits and occluded for 24 hours, all of six animals survived a dose of 5 ml/kg, three of five survived a dose of 7 ml/kg, and one of five survived doses of either 10 or 15 ml/kg. The LD_{50}-value was estimated to be 9 ml/kg. Signs of toxicity following administration of large doses were marked CNS depression and deaths usually occurred within 48 hours after treatment. No appreciable irritation of the skin resulted under these conditions. (Rowe 1947 - quoted from Gingell et al. 1994).

2PG1EEA

No data have been found.

4.1.4 Skin irritation

2PG1EE

In rabbits, the skin reaction consisting of barely perceptible reddening in 2 of 3 rabbits was reported as being minimal and transient; slight flaking of the skin was reported at 72 hours. The test substance was evaluated as being slightly irritating. No further details are given. (BP Chemicals 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

The index of primary cutaneous irritation in rabbits was 1.63, a value equivalent to ‘slightly irritating’ by the criteria utilised in the method. Observations were erythema accompanied by slight, transient oedema; no eschar formation was seen. No further details are given. (BP Chemicals 1981 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EEA

2PG1EEA was evaluated as being slightly irritating to the skin of rabbits (OECD Guideline 404). Two animals showed very slight erythema with or without very

slight oedema on days 2 and 3 only. One animal showed no observable response. (BP Chemicals 1986 – quoted from IUCLID 2000b and ECETOC 1995b).

4.1.5 Eye irritation

2PG1EE

In rabbits (Draize test), signs of irritation consisting of slight discomfort, transient discharge, redness, and chemosis disappeared after 24 hours in one animal. Reversible corneal damage was still evident in two animals at 72 hours. All signs of eye irritation had disappeared after 7 days. The test substance was evaluated as being not irritating. (BP Chemicals 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

When the test substance was instilled in the eyes of rabbits, the index of acute ocular irritation was 48.67 one hour after instillation and decreased steadily to 1.00 by day 7. The test substance was evaluated as being not irritating. (BP Chemicals 1981 – quoted from IUCLID 2000a and ECETOC 1995a).

When the commercial product was applied to the eyes of rabbits on five consecutive days, it caused moderate conjunctival irritation and some transient cloudiness of the cornea. Healing was essentially complete in 3 to 7 days. (Rowe 1947 - quoted from Gingell et al. 1994).

2PG1EEA

2PG1EEA was evaluated as being slightly irritating to the eyes of rabbits (OECD Guideline 405). Initial hyperaemia of the conjunctival membranes was observed which recovered by day 2; there were no effects on either the cornea or iris. (BP Chemicals 1986 – quoted from IUCLID 2000b and ECETOC 1995b).

4.1.6 Skin sensitisation

2PG1EE

No data have been found.

2PG1EEA

No evidence of delayed contact hypersensitivity was observed in the guinea pig maximisation test (OECD Guideline 406). No further details are given. (BP Chemicals 1986 – quoted from IUCLID 2000b and ECETOC 1995b).

4.2 Repeated dose toxicity

4.2.1 Inhalation

2PG1EE

Sprague-Dawley rats (6 males and females per group) were exposed (nose only) to atmospheres containing 1400 or 8900 mg/m^3 for 6 hours per day for 9 days.

According to the citation in ECETOC (1995a), initial exposure resulted in sedation, the effect becoming less marked as the study progressed. The only effect that could be related to treatment was a small increase in liver weight in both sexes exposed to the higher concentration; the livers were histologically normal.
However, according to the citation in IUCLID (2000a), ataxia and reduction in respiratory rate were evident early in exposure to the highest vapour concentration. Female rats experienced reductions in erythrocyte count, haemoglobin concentration and haematocrit, and marginal increase in spleen weight.
(BP Chemicals 1983, 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

Wistar rats (15 males and females per group) were exposed by inhalation (whole body) 6 hours per day, 5 days per week for 13 weeks to atmospheres containing nominally 0, 100, 300, or 2000 ppm (0, 433, 1300, or 8660 mg/m^3). An increase in urine value was observed in both male and female rats exposed to the high concentration during week 1 and to the high and intermediate concentrations during week 12; there were no detectable changes in the composition of either the urine or serum, or histological changes indicative of a toxic effect on the kidney. In animals exposed to the highest concentration, the following effects were observed: irritation of the eyes and nose (minimal and readily reversible); a slight increase in liver weight (females only), the livers were histologically normal; and a small increase in focal macrophage aggregation in the lungs. There were no indications of any adverse effects on either the testes, haematopoietic tissues or blood. (BP Chemicals 1986 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EEA

Wistar rats (5 males and females per group) were exposed by inhalation 6 hours per day, 5 days per week for 28 days to atmospheres containing 0, 102, 292, or 1176 ppm (0, 620, 1775, or 7150 mg/m^3) (OECD Guideline). The concentration of 1176 ppm was the highest droplet free vapour concentration achievable. The only effect observed during the study was a reduced response to external stimuli in animals exposed to high and intermediate concentrations. At the end of the study, comprehensive gross and histopathological examination did not provide any evidence of local or systemic toxicity. The NOAEC was considered (IUCLID) to be > 1176 ppm. (BP Chemicals 1986 – quoted from IUCLID 2000b and ECETOC 1995b).

4.2.2 Oral intake

2PG1EE

Sprague-Dawley rats (6 males and females) were given 10 consecutive oral doses of 2 ml/kg. The body weight gain of the males was slightly reduced compared to controls. A slight increase in liver weight was seen in both sexes and minor haematological changes were reported in males only. The NOAEL was considered (IUCLID) to be < 2000 mg/kg b.w. (BP Chemicals 1983, 1984 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EEA

No data have been found.

4.2.3 Dermal contact

No data have been found.

4.3 Toxicity to reproduction

2PG1EE

No studies regarding reproductive effects have been found.

Rats (25 mated animals per group) were exposed by inhalation (whole body) to nominal vapour concentrations of 0, 100, 450, or 2000 ppm (0, 433, 1950, or 8660 mg/m^3) for 6 hours per day from day 6 to 15 of gestation. According to IUCLID (2000b), the study was conducted using a mixture of PGEE isomers with not less than 92% of 2PG1EE (CAS-no.: 1569-02-4) and not more than 8% of 1PG2EE (CAS-no.: 19089-47-5). Signs of maternal toxicity consisting of reduced body weight gain and food consumption, and of possible irritation were observed in high-dose animals (2000 ppm). In the intermediate group (450 ppm), the body weight gain of the dams was slightly reduced. There was no evidence of maternal effects at 100 ppm. At all exposure concentrations, litter size and weight, the number of pre- and post-implantation losses and mean foetal weights were comparable to controls. No evidence of any effects on foetal development as assessed by incidences of malformations, anomalies, or skeletal variations were observed. The parental and offspring NOAECs were evaluated (IUCLID) as being 100 ppm and > 2000 ppm, respectively. (BP Chemicals 1986 – quoted from IUCLID 2000a and ECETOC 1995a).

Rabbits (22 mated animals per group) were exposed by inhalation (whole body) to nominal vapour concentrations of 0, 100, 350, or 1200 ppm (0, 433, 1515, or 5200 mg/m^3) for 6 hours per day from day 6 to 18 of gestation. According to IUCLID (2000b), the study was conducted using a mixture of PGEE isomers with not less than 92% of 2PG1EE (CAS-no.: 1569-02-4) and not more than 8% of 1PG2EE (CAS-no.: 19089-47-5). Slight maternal toxicity (slight reduction in mean food consumption and a retardation in body weight gain between days 6 and 10 of gestation) was observed at the highest exposure level (1200 ppm). No maternal effects were observed at the lower exposure levels (100 and 350 ppm). No evidence of any treatment related effects on litter size and weight, pre- and post-implantation losses, and mean foetal weights were observed. The overall incidences of malformations were slightly higher in treated animals compared to the controls; the incidences were not dose related and were within the range of the historical control incidences. The parental and offspring NOAECs were evaluated (IUCLID) as being 350 ppm and > 1200 ppm, respectively. (BP Chemicals 1986 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EEA

No data have been found.

4.4 Mutagenic and genotoxic effects

4.4.1 *In vitro* studies

2PG1EE

2PG1EE showed negative results for its potential to produce point mutations in the *Salmonella typhimurium* reverse mutation test using strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation (rat liver post mitochondrial fraction) at doses up to 5000 µg/plate (BP Chemicals 1988 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EE has been evaluated for chromosome damaging potential in cultured human lymphocytes in the presence and absence of post-mitochondrial fraction (S9) at concentrations up to 5000 µg/ml. The frequency of aberrations in treated cells was similar to those in the solvent controls and within the range of the historical solvent controls. (BP Chemicals 1988 – quoted from IUCLID 2000a and ECETOC 1995a).

2PG1EEA

2PG1EEA showed negative results in the reverse mutation test (OECD Guideline 471) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation (rat liver post mitochondrial fraction S9) at doses up to 5000 µg/plate (BP Chemicals 1985 – quoted from IUCLID 2000b and ECETOC 1995b).

Cultured Chinese hamster ovary (CHO) cells were exposed to 2PG1EEA at concentrations up to 2300 µg/ml in the presence and absence of a metabolic activation system (S9). There was no evidence of an increase in the proportion of metaphase figures containing aberrant chromosomes when compared to concurrent controls at any dose level. (BP Chemicals 1985 – quoted from IUCLID 2000b and ECETOC 1995b).

4.4.2 *In vivo* studies

No data have been found.

4.5 Carcinogenic effects

No data regarding carcinogenic effects of 2PG1EE and 2PG1EEA in experimental animals have been found.

5 Regulations

5.1 Ambient air

Denmark (C-value):	2PG1EE: 1 mg/m^3 (MST 2002). 2PG1EEA: 0.01 mg/m^3 (based on odour) (MST 2002).
WHO:	-
US-EPA:	-

5.2 Drinking water

Denmark:	-
WHO:	-
US-EPA:	-

5.3 Soil

Denmark:	-
The Netherlands:	-

5.4 Occupational Exposure Limits

Denmark:	-
ACGIH:	-
Germany:	-

5.5 Classification

-

5.6 IARC

-

5.7 US-EPA

-

6 Summary and evaluation

6.1 Description

2PG1EE and 2PG1EEA are liquids with vapour pressures of 7.5 mmHg (1000 Pa) at 20°C (2PG1EE) and 1.7 mmHg (227 Pa) at 20°C (2PG1EEA). Both substances are highly soluble in water.

6.2 Environment

No data on environmental occurrence have been found.

Tests on aerobic biodegradability in activated sludge showed that 2PG1EE and 2PG1EEA are biodegradable.

6.3 Human exposure

No data have been found.

6.4 Toxicokinetics

No specific data regarding the toxicokinetics of 2PG1EE and 2PG1EEA have been found.

6.5 Human toxicity

No data regarding effects in humans following exposure to 2PG1EE and 2PG1EEA have been found.

6.6 Animal toxicity

6.6.1 Single dose toxicity

LC_{50}-values reported in rats for 2PG1EE are above 14500 mg/m^3 and for 2PG1EEA above 6990 mg/m^3 (as vapour). No evidence of effect on respiratory rate, and by implication sensory irritation, was observed in mice exposed (nose-only) to vapour concentrations of up to 7200 mg/m^3. Oral LD_{50}-values in rats for 2PG1EE and for 2PG1EEA were above 5000 mg/kg b.w. A dermal LD_{50}-value of 9 ml/kg b.w. has been reported for 2PG1EE in rabbits; no data have been found for 2PG1EEA. Signs of toxicity following administration of large doses were CNS depression, and also irritation of eyes and nose following inhalation.

2PG1EE and 2PG1EEA were slightly irritating to the skin of rabbits (2PG1EE: 2 studies; 2PG1EEA: 1 study). 2PG1EE (2 studies) was not irritating to the eyes of rabbits whereas 2PG1EEA (1 study) showed a slightly irritating potential. For

2PG1EEA, no sensitisation was observed in the guinea-pig maximization test; no data have been found for 2PG1EE.

6.6.2 Repeated dose toxicity

In a 90-day inhalation study in rats exposed to 2PG1EE, irritation of the eyes and nose (minimal and readily reversible), a slight increase in liver weight (females only) in the absence of histological changes, and a small increase in focal macrophage aggregation in the lungs were observed at the highest concentration (2000 ppm (8660 mg/m^3)) used in the study. No effects were observed at the lower concentrations (100 and 300 ppm (433 and 1300 mg/m^3). There were no indications of any adverse effects on either the testes, haematopoietic tissues, or blood.
When rats were exposed to 2PG1EEA by inhalation for 28 days, the NOAEC was considered (IUCLID) to be > 1176 ppm (7150 mg/m^3), the highest droplet free vapour concentration achievable.

In rats given 10 consecutive oral doses of 2 ml/kg of 2PG1EE, the body weight gain (males) was slightly reduced; a slight increase in liver weight was seen in both sexes and minor haematological changes were reported in males only. No data regarding the toxicity of 2PG1EEA following oral administration have been found.

6.6.3 Toxicity to reproduction

No studies regarding reproductive effects of 2PG1EE and 2PG1EEA and no studies regarding developmental effects of 2PG1EEA have been found.

In rats and rabbits exposed to 2PG1EE by inhalation (whole body) at concentrations up to 2000 ppm (8660 mg/m^3) (rats) or up to 1200 ppm (5200 mg/m^3) (rabbits), no embryotoxic or foetotoxic effects, including malformations were observed. Maternal effects were observed in rats (450 ppm: slightly reduced body weight gain; 2000 ppm: reduced body weight gain and food consumption, and signs of irritation) and in rabbits (1200 ppm: slight reduction in mean food consumption and a retardation in body weight gain between days 6 and 10 of gestation).

6.6.4 Mutagenic and genotoxic effects

2PG1EE and 2PG1EEA were not mutagenic in the Ames test (five different strains) when tested with and without metabolic activation at concentrations up to 5000 µg per plate.
Negative results have been reported for chromosome aberrations *in vitro* in human lymphocytes (2PG1EE) or Chinese hamster ovary cells (2PG1EEA).
No data regarding a mutagenic potential *in vivo* have been found.

6.6.5 Carcinogenic effects

No data regarding carcinogenic effects of 2PG1EE and 2PG1EEA in experimental animals have been found.

6.7 Evaluation

The toxicological data for 2PG1EE and 2PG1EEA are limited to studies in experimental animals. The studies are only available as internal industrial reports, which have been quoted in IUCLID (2000a,b) and in ECETOC (1995a,b). Below, the effects observed in the studies on 2PG1EE and 2PG1EEA have been compared with the data for the analogue methyl ether (2PG1ME) and methyl ether acetate (2PG1MEA) as summarised in ECETOC (1995d,e) as well as with the data generally known for other glycol ethers as summarised in ECETOC (1995c).

According to ECETOC (1995c), a number of glycol ethers and their acetates have been shown to cause haematological, immunological, testicular, and developmental toxicity; these toxic effects appear to be dependent on the formation of alkoxy acetic acid (from ethylene glycol ethers and their acetates) or alkoxy propionic acid (from certain propylene glycol ethers and their acetates).
Commercial PGEE is a mixture of the α-isomer (2PG1EE or 2PG1EEA) and the β-isomer (1PG2EE or 1PG2EEA). Similarly, commercial PGEEA is a mixture of the α-isomer (2PG1EEA) and the β-isomer (1PG2EEA). The β-isomer, 1PG2EE is probably a substrate for alcohol dehydrogenase resulting in the formation and excretion of ethoxypropionic acid (EPA) and thus having a potential for causing haematological, immunological, testicular, and developmental toxicity. According to ECETOC (1995a,b), the β-isomer usually constitutes less than 10% of commercial PGEE or PGEEA. Generally, no information about the purity of the test substance used in the toxicity studies has been provided except for the developmental studies in rats and rabbits, which (according to IUCLID 2000a,b) were conducted using a mixture of PGEE isomers with *not less than 92% of 2PG1EE (α-isomer) and not more than 8% of 1PG2EE (β-isomer)*.
No metabolic studies with commercial PGEE or PGEEA (or with the pure substances) have been found and thus, it is not known whether the toxic metabolite (EPA) of the β-isomer, 1PG2EE is formed following exposure to commercial PGEE or PGEEA in amounts giving rise to haematological, immunological, testicular, and/or developmental toxicity. However, due to the relatively small percentage (less than 10%) of the β-isomer in commercial PGEE or PGEEA and because the test substance used in the toxicity studies probably is the commercial grade (PGEE, PGEEA) and not the pure α-isomer (2PG1EE, 2PG1EEA), no haematological, immunological, testicular, and developmental effects are expected to arise.

2PG1EE and 2PG1EEA are of low acute toxicity whether animals are exposed via the oral, dermal, or respiratory routes. The substances were slightly irritating to the skin and not irritating (2PG1EE) or slightly irritating (2PG1EEA) to the eyes of experimental animals. No sensitisation was observed when 2PG1EEA was tested in the guinea-pig maximization test.
These results are in concordance with results obtained with the analogue methyl ether (2PG1ME) and methyl ether acetate (2PG1MEA) as summarised in ECETOC (1995d,e) as well as with results obtained with other glycol ethers as summarised in ECETOC (1995c): Generally, glycol ethers exhibit a low to moderate order of acute oral, dermal and inhalation toxicity in rodents. Glycol ethers generally do not appear to be appreciably irritating to the skin on acute exposure; prolonged or repeated skin contact may lead to more severe irritation, consistent with the solvent properties of this chemical class. The majority of glycol ethers showed only slight to moderate eye irritation. There is no indication, from a limited number of animal studies, that glycol ethers cause skin sensitisation.

Following repeated administration (90 days) by inhalation of 2PG1EE to rats, irritation of the eyes and nose (minimal and readily reversible), a slight increase in

liver weight (females only) in the absence of histological changes, and a small increase in focal macrophage aggregation in the lungs were observed at the highest concentration (2000 ppm (8660 mg/m^3)) used in the study; no effects were observed at lower concentrations (100 and 300 ppm (433 and 1300 mg/m^3)). There were no indications of any adverse effects on either the testes, haematopoietic tissues, or blood.
When rats were exposed to 2PG1EEA by inhalation for 28 days, no local or systemic toxicity was observed; the NOAEC was considered (IUCLID 2000b) to be > 1176 ppm (7150 mg/m^3).
These results are in concordance with results obtained with the analogue methyl ether (2PG1ME) and methyl ether acetate (2PG1MEA) as summarised in ECETOC (1995d,e) as well as with results obtained with other glycol ethers as summarised in ECETOC (1995c).

No embryotoxic or foetotoxic effects, including malformations were observed in rats and rabbits exposed to 2PG1EE by inhalation at concentrations up to 2000 ppm (8660 mg/m^3) (rats) or up to 1200 ppm (5200 mg/m^3) (rabbits).
This is in concordance with results obtained with the analogue methyl ether (2PG1ME) and methyl ether acetate (2PG1MEA) as summarised in ECETOC (1995d,e) as well as with results obtained with other glycol ethers as summarised in (ECETOC 1995c) indicating that propylene glycol ethers with the exception of those, which are primary alcohols, do not show developmental toxicity.
The studies on developmental toxicity of 2PG1EE were conducted using a mixture of PGEE isomers with not less than 92% of 2PG1EE (α-isomer) and not more than 8% of 1PG2EE (β-isomer). This indicates that the presence of the potential developmental toxicant, 1PG2EE in commercial PGEE in percentages of up to 8% does not result in developmental effects in rats and rabbits.
No studies regarding testicular effects of 2PG1EE and 2PG1EEA and no reproductive studies have been found. However, there is no evidence that any of the propylene glycol ethers are testicular toxicants (ECETOC 1995c).

The mutagenicity and genotoxicity tests available indicate that 2PG1EE and 2PG1EEA are not mutagenic or genotoxic substances. Similar results have been obtained with the analogue methyl ether (2PG1ME) and methyl ether acetate (2PG1MEA) (ECETOC 1995d,e). Generally, propylene glycol ethers do not appear to have genotoxic potential (ECETOC 1995c).

No carcinogenicity studies have been found. Available data indicate that glycol ethers are unlikely to be carcinogenic (ECETOC 1995c).

6.7.1 Critical effect and NOAEL

The toxicity of 2PG1EE has been more widely studied than that of 2PG1EEA. However, as propylene glycol ether acetates generally are rapidly metabolised to the parent propylene glycol ethers following absorption and as the toxicity of the acetates appears to be very similar to that of their parent ethers, these two substances will be evaluated together.

The toxicological data for 2PG1EE and 2PG1EEA are limited to studies in experimental animals, which only are available as internal industrial reports quoted in IUCLID (2000a,b) and in ECETOC (1995a,b). Based on these data, no critical effects can be pointed out for 2PG1EE or 2PG1EEA. Thus, no health based quality criterion in air can be established for 2PG1EE or 2PG1EEA. However, there are no indications that these substances have a potential for causing haematological, immunological, testicular, and/or developmental toxicity following exposure.

7 Quality criterion in air

No health based quality criterion in air can be established for 2PG1EE and 2PG1EEA.

For 2PG1EEA, an odour threshold (50%) of 0.0089 mg/m^3 has been measured (dk-Teknik 1992). Based on this odour threshold, a C-value of 0.01 mg/m^3 has been set for 2PG1EEA (MST 2002). No odour thresholds in air have been reported for 2PG1EE.

A C-value of 0.01 mg/m^3 and placing in Main Group 2 is proposed for 2PG1EE and for 2PG1EEA individually, as well as for the sum of 2PG1EE and 2PG1EEA.

The proposed C-value is considered to take into account the eventually health based effects following exposure to 2PG1EE and to 2PG1EEA as well as to the two substances in combination as no health based effects have been observed following exposure to 2PG1EE at concentrations up to 1300 mg/m^3 (6 hours per day, 5 days per week for 13 weeks).

7.1.1 C-value

0.01 mg/m^3, Main Group 2 (based on odour).

The C-value is set for 2PG1EE and for 2PG1EEA individually, as well as for the sum of 2PG1EE and 2PG1EEA.

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Evaluation of health hazards by exposure to Propylene glycol 1-ethyl ether and its acetate (2PG1EE and 2PG1EEA) and proposal of a health-based quality criterion for ambient air

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to Propylene glycol 1-ethyl ether and its acetate. This resulted in 2006 in the present report which includes a health-based quality criterion for the substances in ambient air.

Danish Ministry of the Environment
Environmental Protection Agency

Strandgade 29
1401 Copenhagen K, Denmark
Tel.: (+45) 72 54 40 00

www.mst.dk