

Ethylene glycol monoethyl ether¹⁾

[110-80-5]

Supplement 2008

MAK value (2007)	2 ml/m³ \triangleq 7.6 mg/m³
Peak limitation (2001)	Category II, excursion factor 8
Absorption through the skin (1980)	H
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (1994)	Pregnancy risk group B
Germ cell mutagenicity	–
BAT value (1992)	50 mg ethoxyacetic acid/l urine

Chemical name	2-ethoxyethanol
---------------	-----------------

Documentation of the toxicity of ethylene glycol monoethyl ether (from here onwards referred to as EGEE) began in 1983 (documentation “2-Ethoxyethanol” 1983; only available in German) one supplement on the toxicokinetics and reproductive toxicity of EGEE and EGEE acetate was adopted in 1994 (documentation “2-Ethoxyethanol, 2-Ethoxyethyl acetate” 1998, a translation of the 1994 German); a grouped documentation on limitation of exposure peaks was evaluated in a supplement in 2001 (documentation “Ethylene glycol monoethyl ether” 2001, to be published simultaneously with this document). This supplement presents the studies with EGEE and EGEE acetate that pertain to the relevant end points and have been published since that time. The data must be evaluated together since EGEE acetate rapidly hydrolyzes to EGEE, which forms the critical metabolite ethoxyacetic acid. The MAK value also applies to the sum of the concentrations of the two substances in the air.

A BUA report (BUA 1995), IUCLID data sets (ECB 2000 a, b), a review of the Cosmetic Ingredient Review Expert Panel (Johnson 2002), an ECETOC report (ECETOC 2005) and other reviews are available on EGEE and EGEE acetate.

1) MAK value for the sum of the concentrations of ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate in the air

Metabolism and Toxicokinetics

Dermal absorption

EGEE is well absorbed dermally, and has already been described in the 1994 supplement (documentation “2-Ethoxyethanol, 2-Ethoxyethyl acetate” 1998). The dermal absorption of EGEE in vitro (Barber et al. 1992; Lockley et al. 2002; Wilkinson and Williams 2002) and in vivo (see below) was also established in further studies. Since esterification of the alcohol group caused no reduction in the absorption rate through human skin in vitro (Dugard et al. 1984), a high dermal absorption is also assumed for **EGEE acetate**.

A mean permeability coefficient of 19 ± 6 cm/h for EGEE vapour and a dermal flux of 0.7 ± 0.3 mg/cm² and hour for liquid EGEE were found in 5 volunteers who had been exposed to vaporous and liquid EGEE, respectively. This confirms that both vaporous and liquid EGEE are readily absorbed by the skin. When the whole body was exposed to vapours of EGEE, about 42% of the total uptake of EGEE was estimated to be absorbed via the skin. Dermal absorption resulting from 60-minute contact of both hands and forearms (about 2000 cm²) with liquid EGEE would exceed the intake by inhalation of EGEE after 8-hour exposure to 5 ml/m³ by a factor of 20 (Kezic et al. 1997).

After occlusive dermal application of undiluted ¹⁴C-EGEE to the rat skin, 25% of the applied dose was excreted within 24 hours, 15% being excreted in the urine, 6% being exhaled as CO₂ and 1.2% appearing in the faeces; 1.3% remained in the body. Free EGEE, ethoxyacetic acid, ethoxyacetyl glycine and ethylene glycol were detected in the urine (Lockley et al. 2002).

Metabolism

In vitro studies showed that EGEE is also oxidized to ethoxyacetic acid by the isoenzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the rat skin (Lockley et al. 2005).

Biomonitoring

BAT value documentations are available for EGEE and EGEE acetate; a BAT value of 50 mg ethoxyacetic acid/l urine was established in each case (Henschler and Lehnert 1993 a, b).

The metabolite ethoxyacetic acid is responsible for the toxicity of EGEE and EGEE acetate. Since EGEE and EGEE acetate are readily absorbed through the skin and ethoxyacetic acid accumulates in the body because of its long half-life of 21 to 24 hours (Groeseneken et al. 1986 b), the previously available studies in volunteers and exposed workers sometimes revealed very different correlations between the

concentrations of EGEE and EGEE acetate in the air and the excretion of ethoxyacetic acid in the urine (see Table 1). It has meanwhile been possible to calculate a correlation in a PBPK model based on experimental studies. In this compartment-based toxicokinetic model, exposure of workers was simulated for 8 hours per day on 5 days per week until a steady state was reached. Physical activity of 12 hours (8 hours of work and 4 hours of leisure) was assumed followed by a 12-hour phase of rest. A value of 110 μmol ethoxyacetic acid/ mmol creatinine (95th percentile) in biological material corresponding to about 120 mg/l urine was calculated for 8-hour exposure to EGEE at 18 mg/m³ (about 5 ml/m³) (Truchon et al. 2006; see Table 1).

Table 1 Studies of a correlation between the concentrations of EGEE and EGEE acetate in the air and the concentration of ethoxyacetic acid in urine

Cohort		Air	Urine	References
		EGEE or EGEE A (ml/m ³)	Ethoxyacetic acid (mg/l)	
volunteers (n = 5), 4-h exposure	without physical activity	EGEE: 2.7	3.2	Groeseneken et al. 1986 a, b
		EGEE: 5.3	6.0	
		EGEE: 10.7	8.7	
	30 watts	EGEE: 5.3	11.8	
	60 watts	EGEE: 5.3	17.4	
volunteers (n = 5), 4-h exposure	without physical activity	EGEE A: 2.6	2.2	Groeseneken et al. 1987 a, b
		EGEE A: 5.1	4.0	
		EGEE A: 9.8	6.5	
	30 watts	EGEE A: 5.1	7.3	
	60 watts	EGEE A: 5.1	13.7	
female workers (n = 5)		EGEE + EGEE A: 5.0	180 \pm 42 ¹⁾	Veulemans et al. 1987
workers (n = 30)		EGEE A: 12 (2.9–34)	1.3–32 ¹⁾	Lowry et al. 1993
workers in the production of varnishes (n = 12)		EGEE: 2.8	128.5 (PRS); 167.8 (POS)	Angerer et al. 1990
		EGEE A: 2.7		
worker (formulation; n = 19)	Friday	EGEE: 1.9	105.3 (POS)	Angerer et al. 1991
		EGEE A: 2.2		
	Monday	EGEE: 2.0	37.8 (PRS)	
		EGEE A: 0.4		
	Tuesday	EGEE: 1.4	35.9 (POS)	
		EGEE A: 0.1		

Table 1 (Continued)

Cohort		Air	Urine	References
		EGEE or EGEE A (ml/m ³)	Ethoxyacetic acid (mg/l)	
worker (production; n = 19)	Monday	EGEE: 2.9 EGEE A: 0.5	53.2 (PRS)	Söhnlein et al. 1993
	Tuesday	EGEE: 2.1 EGEE A: 0.1	53.8 (POS)	
worker (screen printing; n = 19)		EGEE A: 0.9	8.3	Johanson et al. 1989
PBPK model (exposure 8 hr/d, 5 d/week, 50 watts for 12 h)		EGEE: 5.0	120 ¹⁾ (95th percentile)	Truchon et al. 2006

¹⁾ assuming 1.2 g creatinine/l urine

Key: EGEE: ethylene glycol monoethyl ether

EGEE A: ethylene glycol monoethyl ether acetate;

POS: post-shift;

PRS: pre-shift

Effects in Humans

Allergenic effects

In a patch test, 20 patients with confirmed or suspected contact allergy to cosmetic products were tested with 2% **EGEE** in petrolatum. No signs of irritation were observed, but individual test conditions were not reported (Johnson 2002).

Haematological effects

Two studies that are only available as abstracts were carried out among workers of two factories in Beijing who had been exposed to high concentrations of **EGEE** (no other details); impaired sperm parameters (see below) as well as a decrease in the erythrocyte count, haemoglobin, haematocrit and leukocyte count were reported. The liver function was not impaired (Wang et al. 2003, 2004 b).

An increased incidence of haematological effects (anaemia and granulocytopenia) was observed in a group of 94 workers (shipyard painters) who had been exposed to various substances including **EGEE** and **ethylene glycol monomethyl ether** at mean concentrations of 2.6 and 0.8 ml/m³, respectively, and maximum concentrations of 21.5 and 5.6 ml/m³, respectively. These effects were not found in the group of 55 controls (other shipyard workers) (Welch and Cullen 1988). Additional dermal absorption is assumed but cannot be assessed since no biomonitoring was

mentioned for the measurement of 2-ethoxyacetic acid or 2-methoxyacetic acid concentrations in urine. Therefore, the result of this study can only be used as evidence that ethylene glycol monomethyl ether and EGEE cause haematological effects, but no quantitative assessment can be made.

A group of 32 female workers who had been exposed to **EGEE** revealed urinary concentrations of ethoxyacetic acid of 120.87 mg/g creatinine (geometric mean; about 144 mg/l urine). In the control group of 20 female workers without exposure to EGEE, the urinary excretion of ethoxyacetic acid was 2.71 mg/g creatinine (3.2 mg/l urine). Average erythrocyte counts and haemoglobin levels were normal in both groups. However, 2 women in the exposed group had erythrocyte counts and haemoglobin concentrations that were somewhat lower than the standard levels (Wang et al. 2004 a). Since there is no information about the level of ethoxyacetic acid exposure of these two women and whether menses had any influence, these data cannot be used for the present assessment.

An increased incidence of haematological effects was also observed in a group of 18 shipyard workers (painters) exposed to high concentrations of a solvent mixture containing a geometric mean of 3.0 ml **EGEE acetate**/m³ (maximum: 18.3 ml/m³). The leukocyte count was statistically significantly reduced. However, according to the authors, the reduction was not clinically significant. The geometric mean concentrations of ethoxyacetic acid in the urine of these workers were 9.2 mg/g creatinine (11.0 mg/l urine) with a geometric standard deviation of 5.5 mg/g creatinine (6.7 mg/l urine) and a maximum of 227 mg/g creatinine (272 mg/l urine). A high exposure group consisted of both workers who applied paint in spray form and wore respirators and workers who mixed paint for example and wore no respirators. In a group of 12 workers with low exposure, the leukocyte count was slightly, but not statistically significantly reduced. In this group, the concentration of EGEE acetate in the air was 1.8 ml/m³ (geometric mean; maximum: 8.1 ml/m³), the urinary ethoxyacetic acid concentration was 0.6 mg/g creatinine (0.7 mg/l urine) and the highest concentration was maximally 15 mg/g creatinine (18 mg/l urine). Co-exposure included xylene (28 ml/m³; maximum: about 250 ml/m³) and toluene (12 ml/m³; maximum: about 155 ml/m³) (Kim et al. 1999). The maximum urinary ethoxyacetic acid concentrations of 272 mg/l urine among the workers with higher exposure suggest that individual workers were exposed to a relatively high level. However, since it must be assumed that there were also individual workers in the high exposure group who were exposed to a very low level since preventive measures had been taken and since no correlation was specified between individual exposures and haematological effects, this study is not suitable for making quantitative assessments about the level of exposure at which haematological effects occur.

A group of 29 male and female workers who used **EGEE acetate** as the primary cleaning and printing solvent was examined for haematological effects and compared with 56 controls with low or no exposure. The geometric mean of the concentration of EGEE acetate in the air was 7.41 ml/m³ (range: 1.35–15.5 ml/m³), but it had been 45.51 ml/m³ (workplaces of the male workers) and 38.82 ml/m³ (workplaces of the female workers) 4 months before the study. The current mean

exposure of the 12 female workers at the manual printing machines was significantly higher (geometric mean: 9.34 ml/m³) and longer (8 h/d) than that of the 17 male workers (geometric mean: 4.87 ml/m³; 2.4 h/d) at the automatic printing machines. Haemoglobin and haematocrit levels of the female workers were significantly lower than those in the control group, and there was a concentration-response relationship. No difference was found between the male workers and the control group (Loh et al. 2003). Additional dermal absorption must be assumed for the female workers since they wore no protective gloves; respirators were provided for the male workers. Since no biomonitoring was carried out, no quantitative assessment can be made.

Fertility

There are several studies among workers in the semiconductor industry who were exposed to ethylene-based glycol ethers and their acetates (ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate; EGEE and EGEE acetate) and to propylene-based glycol ethers, xylene and n-butyl acetate (Gray et al. 1996; Ha et al. 1996; Lamm et al. 1996; Schenker 1996; Schenker et al. 1995; Swan et al. 1995). Since all studies assessed the exposure to ethylene-based glycol ethers together, no distinction can be made from exposure to ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate, whose developmental toxicity (teratogenicity) and adverse effect on fertility were more pronounced in animal studies than those of EGEE and EGEE acetate (Nelson et al. 1984). Nor were any concentrations of glycol ethers in the air or biomonitoring studies mentioned. Therefore, these studies cannot be used for the present assessment.

Male fertility

Evidence of a spermatotoxic effect was provided for EGEE and EGEE acetate among exposed workers.

Exposure of 73 workers employed as painters in a shipyard included **EGEE** (mean: 2.6 ml/m³; median: 1.2 ml/m³; maximum: 21.5 ml/m³) and **ethylene glycol monomethyl ether** (mean: 0.8 ml/m³; median: 0.44 ml/m³). The results of a sperm analysis indicated that exposure to glycol ethers had an effect on the sperm count. Although the mean for the sperm count/ejaculation ($158 \times 10^6/\text{ml}$) was not significantly different for the exposed group from that of the control group ($211 \times 10^6/\text{ml}$), according to the authors, there were biologically important differences in the incidence of oligospermia (13.5%; control: 5%) and azoospermia (5%; normal population: 1%) (Welch et al. 1988; see documentation "2-Ethoxyethanol, 2-Ethoxyethyl acetate" 1998, a translation of the 1994 German). Additional dermal absorption is assumed but cannot be assessed since no biomonitoring was mentioned for the measurement of ethoxyacetic acid or methoxyacetic acid concentrations in the ur-

ine. No quantitative assessment can therefore be made as to which exposures lead to changes in sperm parameters.

In a cross-sectional study, which was used for deriving the MAK value in 1994, the average sperm count per ejaculate was statistically significantly lower among 37 workers exposed to EGEE than that of 38 controls after consideration of confounders such as abstinence, sample age, subjects' age, tobacco consumption, alcohol and caffeine use, urogenital disorders, fever and other illnesses. No significant differences in semen volume and concentration, semen pH, viability, motility and velocity, semen morphology or testicular volume were observed. The proportion of men with oligozoospermia was higher in the exposed group (16.2%) than in the control group (10.5%), but this difference was not statistically significant. The currently measured exposure concentrations of EGEE ranged from "not detectable" to 24 ml/m³ with a geometric mean of 6.6 ml/m³. However, exposure to EGEE had been reduced in 2 of 3 buildings 2 to 3 weeks before the study: There was a reduction from 16.9 to 3.0 ml/m³ in building A; the airborne levels of 10.7 and 14.9 ml/m³ remained the same in building B, and in building C there was a reduction from about 16.9 to 2.4 ml/m³ as in building A. Measurements of the urinary metabolite ethoxyacetic acid during the study yielded concentrations between "not detectable" and 163 mg/g creatinine (about 196 mg/l urine assuming 1.2 g creatinine/l urine). In a subgroup of 10 workers with relatively high current urinary ethoxyacetic acid concentrations of 85 ± 31.3 mg/g creatinine (about 100 mg/l urine assuming 1.2 g creatinine/l urine), a regression analysis revealed no differences in the semen parameters of workers with lower current exposure as compared with non-exposed workers (Ratcliffe et al. 1989). The number of 10 workers in this group may have been too small to detect effects. It is also problematical that the workers were divided into exposure or control group based on the urinary ethoxyacetic acid concentrations measured during the study. Effects due to previous exposure could thus not be ruled out in workers of the control group. Possible differences might thus have been less marked. Since the reduction in exposure in two of the three buildings occurred within the period of an average spermatogenic cycle of 70 days, effects on the sperm would still have been observed at the time of the study irrespective of the currently measured exposure concentrations in the air or urine. Because of the limitations of this study, effects at 85 ± 31.3 mg ethoxyacetic acid/g creatinine (about 100 mg/l urine) cannot be ruled out. In spite of its limitations, the study shows that effects on sperm parameters result at EGEE concentrations of up to about 17 ml/m³.

On account of the small number of exposed workers in the two studies described above (Ratcliffe et al. 1989; Welch et al. 1988) and their resulting lower statistical validity, the two studies were evaluated together. The assessment revealed significant effects on sperm concentration and semen volume (Schrader et al. 1996). However, no quantitative statements were made about effect levels of EGEE concentrations in the air or ethoxyacetic acid concentrations in the urine.

In a case-control study, 1019 patients with reproductive disorders who were diagnosed infertile or subfertile on the basis of their spermograms ("cases") were compared with 475 patients with reproductive disorders who were assessed as

normally fertile on the basis of their spermograms ("controls"). **Ethoxyacetic acid** was measured in the urine of 39 of the 1019 "cases" (3.8%) at a significantly higher rate than in the urine of 6 of the 475 "controls" (1.3%) at concentrations of 1.3 to 71 mg/l. Methoxyacetic acid was found in only one "case" and two "controls". Oligozoospermia was found in 43 of the 45 persons with evidence of ethoxyacetic acid in the urine ("cases" and "controls"); 11 of them revealed azoospermia. There was no significant correlation between the concentrations of ethoxyacetic acid determined in the urine and various sperm quality parameters. In the opinion of the authors, the lack of such a correlation could be explained by the expected latency between exposure and the occurrence of observable effects. In addition, the frequency and duration of exposure and the period between last exposure and measurement of the ethoxyacetic acid concentration in the urine was inadequately characterized (Veulemans et al. 1993; see (documentation "2-Ethoxyethanol, 2-Ethoxyethyl acetate" 1998, a translation of the 1994 German).

In two studies, which were however only published as abstracts, significantly reduced sperm counts were observed among workers of two factories in Beijing who had been exposed to high concentrations of **EGEE** (no other details). Progressive motility and the proportion of sperm with normal morphology were significantly lower than in the control group. Haematological parameters were also decreased (see "Haematological effects"). There were no differences in sex hormones in the blood, luteinizing hormone, follicle-stimulating hormone, prolactin or oestradiol (Wang et al. 2003, 2004 b).

Female fertility

Various studies are available on the fertility of women who were employed in the semiconductor industry or in chip production. Increased relative risks of spontaneous abortions and lower fertility were reported (Chen et al. 2002; Correa et al. 1996; Gray et al. 1996; Hsieh et al. 2005; Lamm et al. 1996; Schenker 1996; Schenker et al. 1995; Swan and Forest 1996; Swan et al. 1995). These studies cannot be used for the present assessment because, as mentioned before, ethylene-based glycol ethers were assessed together in these studies, no distinction was made between ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate and the glycol ether concentrations were not measured in the air, nor was biomonitoring performed.

The menstrual cycles of 52 female workers in the LCD manufacturing industry were compared with those of 55 female workers from other areas of the factory. No significant differences were observed with regard to the period of the menstrual cycle, the duration of the menses and the amount of flow even after adjustment. However, at 0.51 ml/m³ (geometric mean), the exposure concentration of **EGEE acetate** was relatively low. The urinary excretion of ethoxyacetic acid was 0.12 mg/g creatinine (geometric mean) at the start of shift and 0.16 mg/g creatinine at the end of shift, and therefore also very low (Chia et al. 1997).

Developmental toxicity

Although several studies were carried out to examine the effect of occupational exposure to glycol ethers on the occurrence of congenital malformations, none of them allow conclusions to be drawn about a possible developmental toxicity of EGEE since exposure to individual glycol ethers was not recorded.

In a Europe-wide case-control study, a total of 984 cases of one or several major congenital malformations were recorded between 1989 and 1992 including 222 induced abortions, 42 stillbirths and 720 children who were found to have malformations during their first week of life. One or two controls (live offspring without malformations from the same hospital) were selected for each case. An overall association was observed between exposure to glycol ethers (in general) and all malformations (OR: 1.4; 95% CI: 1.1–1.9). There was a particular association between exposure to glycol ethers and neural tube defects (OR: 1.94; 95% CI: 1.16–3.24), multiple anomalies (OR: 2.00; 95% CI: 1.24–3.23) and cleft lips (OR: 2.03; 95% CI: 1.11–3.73). The OR for cleft lips increased with the level of exposure (Cordier et al. 1997; Ha et al. 1996).

The same working group carried out a case-control study with a similar design in the Slovak Republic. The study comprised 107 cases (live or stillborn children and therapeutic abortions) with severe malformations and 131 children without malformations as controls. After exposure to glycol ethers, the adjusted OR of 2.3 (95% CI: 0.7–7.0) was increased, although not significantly, for all congenital malformations (Cordier et al. 2001).

In a case-control study comprising 538 children with special malformations (anencephaly, spina bifida, craniorachischisis and iniencephaly) and 539 controls, the mothers were exposed to 74 chemicals including glycol ethers during pregnancy. Maternal exposure to glycol ethers showed no association with the malformations (Shaw et al. 1999).

PBPK models

Physiologically based pharmacokinetic (PBPK) models were developed for EGEE and EGEE acetate for humans and for pregnant rats. PBPK models of EGEE acetate (Gargas et al. 2000; Hays et al. 1999), data of a study on the developmental toxicity of EGEE in rats (Doe 1984; NOAEC: 50 ml/m³) and data from a volunteer study with 4-hour exposure to EGEE or EGEE acetate (Groeseneken et al. 1986 a, b, 1987 a, b) were used for this purpose. The models considered five compartments, rapid hydrolysis of EGEE acetate to EGEE, metabolism of EGEE to ethoxyacetic acid and urinary excretion of ethoxyacetic acid. Based on the NOAEC of 50 ml/m³ for developmental toxicity in rats, the physiological parameters of the rat were compared with those of a pregnant woman and a NAEC was calculated from these for humans. NAECs of 25 ml/m³ were derived for both substances. The authors suggested an 8-hour limit value of 2 ml/m³, taking into account safety factors (2.5

for interspecies extrapolation, 3.16 for inter-individual variability and 1.8 for pharmacokinetic intra-species differences) (Sweeney et al. 2001).

Genotoxicity

Two groups of 19 workers exposed to EGEE (2.9 ml/m³), EGEE acetate (0.5 ml/m³) and **ethylene glycol monobutyl ether** (0.5 ml/m³) had urinary ethoxyacetic acid and butoxyacetic acid concentrations of 53.2 and 0.2 mg/1 urine on Monday before the shift and respectively, of 53.8 and 16.4 mg/1 urine on Tuesday after the shift. The numbers of SCEs and micronuclei were not increased in lymphocytes that had been obtained from blood samples collected on Tuesday after the shift (Söhnlein et al. 1993).

Animal Experiments and *in vitro* Studies

Subacute, subchronic and chronic toxicity

Haematopoietic and lymphatic organs, the testicular seminiferous epithelium, kidneys and liver are the main target organs of the toxicity of EGEE (BUA 1995). The results of relevant studies on the inhalation and ingestion of EGEE and EGEE acetate are summarized in Table 2 and Table 3, respectively.

Table 2 Studies with repeated inhalation and ingestion of EGEE in rats, mice, rabbits and dogs

Species, strain, No. of animals per group	Exposure	Findings	References
inhalation			
rat , Sprague Dawley, 15 ♂ and 15 ♀	13 weeks , 0, 25, 100, 400 ml/m ³ , 6 h/d, 5 d/week	400 ml/m³ : NOAEC	Barbee et al. 1984
rabbit , white New Zealand, 10 ♂ and 10 ♀	13 weeks , 0, 25, 100, 400 ml/m ³ , 6 h/d, 5 d/week	100 ml/m³ : NOAEC 400 ml/m³ : b.w. gain ↓; haemoglobin, haematocrit and erythrocyte count ↓; testicular changes	Barbee et al. 1984
ingestion			
rat , F344, 30 ♂	13 weeks , 0, 109, 205, 400, 792, 2240 mg/kg b. w. and d, drinking water	109 mg/kg b.w. : NOAEL at 205 mg/kg b.w and above. : b.w. gain ↓; thrombocytopenia; absol. and rel. thymus weights ↓; atrophy of prostate at 400 mg/kg b.w. and above : testicular	NTP 1993

Table 2 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
		atrophy; haematopoiesis in the spleen; anaemia; total protein ↓ at 792 mg/kg b.w. and above: leukopenia; leukocytosis; thymic atrophy; haemosiderin deposits and haematopoiesis in the liver; bone marrow hyperplasia; albumin concen- tration ↓; rel. and abs. testis weights ↓, epididymis weight ↓; aspermia 2240 mg/kg b.w.: mortality ↑ (5/10); hae- mosiderin deposits in the spleen	
rat, F344, 30 ♀	13 weeks, 0, 122, 247, 466, 804, 2061 mg/kg b.w. and d, drink- ing water	466 mg/kg b.w.: NOAEL at 804 mg/kg b.w. and above: b.w. gain ↓; absol. and rel. thymus weights ↓; leukope- nia; leukocytosis; thymic atrophy; haemosi- derin deposits in the liver; albumin concen- tration ↓; length of oestrous cycle ↓ 2061 mg/kg b.w.: mortality ↑ (7/10); hae- mosiderin deposits in the spleen	NTP 1993
rat, 10; no other details	13 weeks, 52–1890 mg/kg b.w. and d, drink- ing water	210 mg/kg b.w.: NOAEL at 740 mg/kg b.w. and above: b.w. gain ↓; water consumption ↓; changes of liver and kidney weights; histopathological changes in the liver, kidney, spleen or testes (no other details) 1890 mg/kg b.w.: mortality ↑	Smyth et al. 1951
rat, Wistar, 5 ♂ and 5 ♀	13 weeks, 0, 46, 93, 186 mg/ kg b.w. and d; from day 56. 0, 46, 372, 743 mg/kg b.w. and d; no other details	93 mg/kg b.w.: NOAEL 93/372 mg/kg b.w.: haemoglobin and haematocrit ↓ at 186 mg/kg b.w. and above: haemosi- derin deposits in the spleen; testicular changes (oedematous and disintegrating interstitium; absence of advanced ma- turation stages of spermatogonia and spermocytes)	Stenger et al. 1971
rat, F344, 50 ♂ and 50 ♀	103 weeks, 0, 500, 1000, 2000 mg/kg b.w. and d, 5 d/week, gavage	500 mg/kg b.w.: ♂ and ♀: b.w. gain ↓; in- cidence of animals with enlarged spleens and pituitary changes ↑; ♂: testicular atrophy; enlarged adrenal; ♀: subcutaneous tissue in the mamma ↓ 1000 mg/kg b.w.: ♂: mortality ↑	Melnick 1984

Table 2 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
		2000 mg/kg b.w.: ♂ and ♀: mortality ↑; gastric ulcerations; exposure terminated after 17–18 weeks; ♂: testicular atrophy (no other details) histopathological examinations of the testes of animals of the high exposure group only	
mouse, JCL-ICR, 5 ♂	5 weeks, 0, 500, 1000, 2000, 4000 mg/kg b.w. and d, 5 d/week, gavage	500 mg/kg b.w.: NOAEL at 1000 mg/kg b.w. and above: testicular atrophy; absol. and rel. testis weights ↓ 2000 mg/kg b.w.: leukocyte count ↓ 4000 mg/kg b.w.: 100% mortality	Nagano et al. 1979
mouse, B6C3F ₁ , 10 ♂ and 10 ♀	13 weeks, 0, 587, 971, 2003, 5123, 7284 mg/kg b.w. and d, drink- ing water	2003 mg/kg b.w.: NOAEL at 5123 mg/kg b.w. and above: b.w. gain ↓, absol. testis weight ↓ 7284 mg/kg b.w.: testicular degeneration; haematopoiesis in the spleen ↑	NTP 1993
mouse, B6C3F ₁ , 10 ♀	13 weeks, 0, 722, 1304, 2725, 7255, 11 172 mg/ kg b.w. and d, drinking water	1304 mg/kg b.w.: NOAEL at 2725 mg/kg b.w. and above: adrenal hypertrophy 7255 mg/kg b.w.: b.w. gain ↓; haemato- poiesis in the spleen ↑	NTP 1993
mouse, B6C3F ₁ , 50 ♂ and 50 ♀	103 weeks, 0, 500, 1000, 2000 mg/kg b.w. and d, 5 d/week, gavage	500 mg/kg b.w.: ♂ and ♀: b.w. gain ↓ 1000 mg/kg b.w.: ♂: testicular atrophy 2000 mg/kg b.w.: ♂ and ♀: mortality ↑; ex- posure terminated after 17–18 weeks; ♂: gastric ulcerations; testicular atrophy ↑ (no other details) histopathological examinations of the testes of animals of the high exposure group only	Melnick 1984
dog, beagle, 3 ♂ and 3 ♀	13 weeks, 0, 46, 93, 186 mg/ kg b.w. and d, 7 d/ week, gelatin cap- sule	46 mg/kg b.w.: NOAEL at 93 mg/kg b.w. and above: haemoglo- bin and haematocrit ↓ 186 mg/kg b.w.: slight kidney changes (3/6); testicular changes (<i>e.g.</i> absence of the advanced maturation stages of the seminiferous epithelium)	Stenger et al. 1971

Table 3 Studies with repeated inhalation and ingestion of EGEE acetate in rats, rabbits, mice and dogs

Species, strain, No. of animals per group	Exposure	Findings	References
inhalation			
rat, Wistar, 10 ♂ and 10 ♀	10 months, 0, 200 ml/m ³ , 4 h/d, 5 d/week	200 ml/m³: ♂: nephritis with degenera- tions of the epithelium; ♀: NOAEC N.A.D.: body weight gain, haematology, urinalysis and gross pathology	Truhaut et al. 1979
rabbit, white New Zealand, 10 ♂ and 10 ♀	10 months, 0, 200 ml/m ³ , 4 h/d, 5 d/week	200 ml/m³: ♂, ♀: slight kidney changes N.A.D.: body weight gain, haematology, urinalysis and gross pathology	Truhaut et al. 1979
dog, no other details	24 weeks, 0, 600 ml/m ³ , 7 h/d, 5 d/week	600 ml/m³: no effects	ECB 2000 b
ingestion			
mouse, JCL-ICR, 5 ♂	5 weeks, 0, 500, 1000, 2000, 4000 mg/kg b.w. and d, 5 d/week, gavage	500 mg/kg b.w.: no effects (NOAEL) at 1000 mg/kg b.w. and above: testicular atrophy; absol. and rel. testis weights ↓ 2000 mg/kg b.w.: leukocyte count ↓, re- duced number of spermatozoa, sperma- tids and spermatocytes 4000 mg/kg b.w.: 100% mortality	Nagano et al. 1979

N.A.D. = no abnormality detected

Inhalation

In 13-week inhalation studies carried out with **EGEE** using a sufficient scope of examination (body weight gain, haematological and clinicochemical parameters and ophthalmological and histopathological examinations), no alterations were observed in rats up to 400 ml/m³ (NOAEC). Changes in the blood count and in the testes were observed in rabbits at 400 ml/m³; the NOAEC for EGEE is 100 ml/m³ (Barbee et al. 1984; Table 2).

Inhalation studies carried out with **EGEE acetate** in rats and rabbits for 10 months revealed nephritis in male rats and slight kidney changes in rabbits at the only tested concentration of 200 ml/m³ (Truhaut et al. 1979; Table 3). No effects were observed in an inhalation study with up to 24-week exposure carried out in dogs at the only investigated concentration of 600 ml/m³ (ECB 2000 b; Table 3).

Ingestion

Male rats proved to be more sensitive to the haematotoxic effect of **EGEE** than female rats. In a 13-week study, the NOAEL for male and female rats was 109 and

466 mg/kg body weight and day, respectively. Doses of 205 mg/kg body weight and day and above led to thrombocytopenia in male animals, reduced absolute and relative thymus weights and reduced body weight gains; doses at 400 mg/kg body weight and day and above induced testicular atrophy and anaemia. Doses of 792 mg/kg body weight and day in males and 804 mg/kg body weight in females revealed leukopenia, leukocytosis, thymic atrophy, haemosiderin deposits in the liver and a reduced albumin concentration (NTP 1993; Table 2).

In studies with 5-week administration of **EGEE** or **EGEE acetate** in mice, a NOAEL of 500 mg/kg body weight and day was obtained for both substances; testicular atrophy was observed from 1000 mg/kg body weight and day (Nagano et al. 1979; Table 2 and Table 3). In 13-week studies with **EGEE** in mice, a NOAEL of 1304 mg/kg body weight and day and 2003 mg/kg body weight and day was obtained for males and females, respectively, the females thus being more sensitive than males. Adrenal hypertrophy occurred in females from 2725 mg/kg body weight and day, and reductions in body weight gains and absolute testicular weights were observed in males from 5123 mg/kg body weight and day. Doses of more than 7000 mg/kg body weight and day led to increased haematopoiesis in the spleen of males and females and to testicular degeneration in males (NTP 1993; Table 2). In a 103-week study, testicular atrophy was observed in male mice at a concentration of **EGEE** from as low as 1000 mg/kg body weight (Melnick 1984; Table 2).

A NOAEL of 46 mg/kg body weight and day for **EGEE** showed that dogs were the most sensitive species investigated. Haemoglobin and haematocrit were reduced from 93 mg/kg body weight and day, and slight kidney changes were observed in males and females, and testicular changes in males, at 186 mg/kg body weight (Stenger et al. 1971; Table 2).

Local effects on skin and mucous membranes

Skin

The 24-hour occlusive application of 0.5 ml **EGEE** to the clipped intact dorsal skin of rabbits led to slight irritation (0.6 of 23). In a different study, **EGEE** was assessed as non-irritating after application of the same concentration of 0.5 ml to the shaved intact dorsal skin of rabbits for 4 hours (no data on occlusion). A further study demonstrated that the open dermal application of 500 mg **EGEE** (about 0.5 ml) led to slight irritation (BUA 1995).

After occlusive application of **EGEE acetate** to the intact and abraded rabbit skin, only slight irritation was also observed after 24 hours (1 of 4); after 72 hours, there was hardly any irritation (0.08 of 8). **EGEE acetate** caused slight irritation in two further studies, whereas the substance was described as non-irritating to the rabbit skin in another test procedure (BUA 1995).

Eyes

The instillation of 0.1 ml **EGEE** into the conjunctival sac of rabbits revealed moderate irritation (median 20.8 of 110). Weak irritation (maximally 3 of 10) was also observed after instillation of 0.005 to 0.5 ml (BUA 1995).

After instillation of 0.1 ml of a 30% solution and of undiluted **EGEE acetate** into the conjunctival sac of rabbits, slight irritation (3 and 15 of 110, respectively) was recorded 24 hours after application. EGEE acetate was assessed as non-irritating in two other Draize tests in rabbits (BUA 1995).

Allergenic effects

EGEE showed no sensitizing potential in a maximization test carried out according to Magnusson and Kligman (BUA 1995).

In a further maximization test carried out according to Magnusson and Kligman in a total of 30 Dunkin-Hartley guinea pigs, **EGEE** and **EGEE acetate** revealed no sensitization either (Johnson 2002).

Reproductive toxicity

Fertility

The toxic effect of EGEE and EGEE acetate on the reproductive tract has been well documented in animal studies. For example, reduced testis weights and a slight degeneration of the seminiferous tubules were observed in a 13-week inhalation study with **EGEE** in rabbits from 400 ml/m³. The NOAEC was 100 ml/m³ (Barbee et al. 1984). Testicular atrophy was observed from 400 mg/kg body weight and day in studies in rats that were given **EGEE** orally for 13 weeks (administration in the drinking water; NTP 1993) or from 186 mg/kg body weight and day (administration by gavage; Stenger et al. 1971). The NOAELs in the two 13-week studies were 109 and 93 mg/kg body weight and day (see Table 2). In a further study, **EGEE** was administered orally by gavage to 5-week-old juvenile rats and 9-week-old adult rats over a period of 4 weeks at doses of 0, 50, 100, 200 and 400 mg/kg body weight and day. Slightly increased relative testis and epididymis weights were observed in juvenile rats even at the lowest dose of 50 mg/kg body weight and day and above, although they were not related to the dose and were not statistically significant, whereas these weights were statistically significantly reduced in adult rats at 400 mg/kg body weight and day. The cytometric analysis of testicular cell populations revealed reduced proportions of mature (elongated spermatids) and immature haploid cells (round and elongated spermatids) and increased proportions of diploid (spermatogonia, secondary spermatocytes and somatic cell tissue) and tetraploid cells (primary spermatocytes) only in adult rats at 400 mg/kg body weight and day (Yoon et al. 2001). Administration of EGEE to 8-week-old rats for 4 weeks led to reduced body weight gains from 200 mg/kg body weight and day and to reduced epididymis weights from as low as 100 mg/kg body weight and day. Histopathological

testicular changes were observed at 200 and above mg/kg body weight and day (Yoon et al. 2003).

When **EGEE** was administered to 12-week-old Sprague Dawley rats for 5 weeks at doses of 0, 100, 300 and 600 mg/kg body weight and day, significantly reduced sperm motility was observed at the high dose level (Wang et al. 2006).

The up to 7-week administration of **EGEE** to 10- to 15-week-old rats at doses of 0, 250 and 500 mg/kg body weight and day led to reduced body weight gains at 250 mg/kg body weight and day and to body weight losses at 500 mg/kg body weight and day. From 250 mg/kg body weight and day, the relative and absolute testis and epididymis weights were reduced, and there were changes in sperm parameters such as a reduced sperm count and impaired motility. After 7-week administration of 500 mg/kg body weight and day, the sperm count was considerably decreased ($34 \times 10^6/g$ testis as compared with the control of $883 \times 10^6/g$), and the sperm were no longer motile (Horimoto et al. 2000; Isobe et al. 1996).

In a one-generation study in CD-1 mice with continuous mating, groups of 40 males and 40 females were given 0, 0.5, 1.0 and 2% **EGEE** in the drinking water for 14 weeks, corresponding to 0, 760, 1500 and 2600 mg/kg body weight and day. All offspring were examined immediately after birth. Fertility was impaired from 1500 mg/kg body weight and day. Reduced absolute testis and epididymis weights and morphological sperm changes as well as a considerably reduced number of live offspring and reduced body weights of the offspring were observed. No dam became pregnant at 2600 mg/kg body weight and day, and the oestrus cycle was prolonged (Lamb et al. 1984, 1997).

EGEE acetate was also examined in a one-generation study in CD-1 mice with continuous mating by the NTP (1993). The animals were given the substance in the drinking water for 18 months. The doses corresponded to 0, 900, 1800 and 3000 mg/kg body weight and day. The number of litters and the number of live offspring was reduced at 1800 mg/kg body weight and above; the results of cross-mating experiments showed that this was due mainly to the exposure of females. Effects on sperm parameters, testis weights and the incidence of abnormal sperm were less pronounced than the effects on female fertility (no other details) (ECB 2000 b).

Developmental toxicity

Studies of the developmental toxicity of **EGEE** and **EGEE acetate** are summarized in Table 4 and Table 5, respectively. Since these are often older studies from the 1970s and 1980s, prior to the standardization of the terminology used for skeletal and visceral changes, the terminology of the publications is adopted.

Prenatal developmental toxicity

The most important studies of prenatal developmental toxicity have already been described in the 1994 supplement (documentation "2-Ethoxyethanol, 2-Ethoxyethyl acetate" 1998, a translation of the 1994 German).

Table 4 Studies of pre- and postnatal developmental toxicity of EGEE

Species, strain, No. of animals per group	Exposure	Findings	References
<u>Prenatal developmental toxicity</u>			
inhalation			
rat, Wistar, 29–38 ♀	3 weeks before mat- ing/GDs 1–19, 0/0, 150/0, 649/0, 0/202, 150/202, 0/767, 649/ 767 ml/m³, 7 h/d, 5 d/ week, exam on GD 21	150/0 and 649/0 ml/m³: dams and foetuses: no effects 0/202 and 150/202 ml/m³: dams: no effects; foetuses: foetal weight ↓, crown-rump length ↓, anomalies ↑ (“minor”: altered morphology of ribs and cardiovascular defects) and variations ↑ (extra ribs and retarded ossification) 0/767 and 649/767 ml/m³: dams: b.w. gain ↓; foetuses: total resorptions	Andrew and Hardin 1984
rat, Wistar, 24 ♀	GDs 6–15, 0, 10, 50, 250 ml/m³, 6 h/d, exam on GD 21	50 ml/m³: NOAEC 250 ml/m³: dams: anaemia; foetuses: external and visceral defects (“minor”: mainly dilated renal pelvis) ↑ and skeletal defects (“minor”) ↑	Doe 1984
rabbit, Dutch, 24 ♀	GDs 6–18, 0, 10, 50, 175 ml/m³, 6 h/d, exam on GD 29	50 ml/m³: NOAEC 175 ml/m³: dams: no effects; foetuses: skeletal defects (“minor”) and variations ↑	Doe 1984
rabbit, white New Zealand, 29–38 ♀	GDs 1–18, 0, 160, 617 ml/m³, 7 h/ d, exam on GD 29	160 ml/m³: dams: feed consumption distinctly ↓, rel. liver weight ↑; foetuses: number of live foetuses ↓, number of resorptions ↑, malformations ↑, anoma- lies ↑ and variations ↑ 617 ml/m³: dams: mortality ↑, b.w. ↓ and rel. kidney weight ↑; foetuses: total resorptions	Andrew and Hardin 1984
ingestion			
rat, SD, n.s.	GDs 7–15, 0, 200 mg/kg b.w. and	200 mg/kg b.w.: dams: b.w. gain ↓; foetuses: foetomortality ↑, foetal weight ↓	Goad and Cranmer 1984

Table 4 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
	d, gavage, exam on GD 20	and skeletal and cardiovascular (24%) anomalies ↑	
rat, n.s., 8–19 ♀	GDs 7–17, 0, 210–550 mg/kg b.w. and d, drinking water, exam on GD 21	210–270 mg/kg b.w.: 31% embryomortal- ity 270–400 mg/kg b.w.: 69% embryomortal- ity and foetal weight ↓; no malformations 400–550 mg/kg b.w.: 100% embryo- mortality	Chester et al. 1986
rat, Wistar at least 20 ♀	GDs 1–21, 0, 12, 23, 47, 93, 186, 372 mg/kg b.w. and d, gavage, exam on GD 22	23 mg/kg b.w.: NOAEL 47 mg/kg b.w.: total proportion of foetuses with skeletal findings ↑ (5.3%; control: 2.7%) at 93 mg/kg b.w. and above: total propor- tion of foetuses with skeletal findings ↑ (21.1%; control: 2.7%) and foetal weight ↓ 186 mg/kg b.w.: total proportion of foe- tuses with skeletal findings ↑ (88.8%; con- trol: 2.7%; mainly incompletely ossified cal- varia, aplasia of hyoid, thoracic and lumbar schisis, partial aplasia of the sternum and wavy ribs) and proportion of live foetuses ↓; no severe malformations	Stenger et al. 1971
mouse, CD-1, 6 ♀	GDs 8–14, 0, 1000, 1800, 2600, 3400, 4200 mg/kg b.w. and d, exam on GD 22	1000 mg/kg b.w.: foetuses: foetal weight ↓ 1800 mg/kg b.w.: dams: b.w. gain ↓; foetuses: resorptions ↑ and malformations ↑ (fused, small or absent digits of front paws, exencephaly and cleft palates) 3400 mg/kg b.w.: dams: mortality ↑ 4200 mg/kg b.w.: 100% resorption rate	Wier et al. 1987
subcutaneous injection			
rat, Wistar at least 20 ♀	GDs 1–21, 0, 23, 47, 93 mg/kg b.w. and d, exam on GD 22	23 mg/kg b.w.: NOAEL 47 mg/kg b.w.: total proportion of foetuses with skeletal aberrations ↑ (6.2%; control: 3.6%) at 93 mg/kg b.w. and above: total propor- tion of foetuses with skeletal aberrations ↑ (27.8%; control: 3.6%)	Stenger et al. 1971

Table 4 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
mouse, Swiss, 22 ♀	GDs 1–18, 0, 47, 93 mg/kg b.w. and d, exam on GD 19	93 mg/kg b.w.: NOAEL	Stenger et al. 1971
rabbit, Gelbsilber, 15 ♀ expos. and 8 ♀ contr.	GDs 7–16, 0, 23 mg/kg b.w. and d, exam on GD 29	23 mg/kg b.w.: NOAEL	Stenger et al. 1971
dermal			
rat, SD, 18 ♀	GDs 7–16, 4 × daily 0, 0.25, 0.5 ml/application (about 0, 1, 2 ml/day), about 0, 3445, 6889 mg/kg b.w. and d, exam on GD 21	3445 mg/kg b.w.: <u>dams:</u> b.w. gain ↓; <u>foetuses:</u> 50% total resorptions, foetal weight ↓, visceral (heart, kidney, brain and eyes) and skeletal malformations and varia- tions 6889 mg/kg b.w.: <u>dams:</u> ataxia and absol. liver weight ↓; <u>foetuses:</u> 100% total resorptions	Hardin et al. 1982, 1984
Postnatal developmental toxicity			
inhalation			
rat, SD, 59 ♀ (main study)	GDs 7–13 or GDs 14–20, <u>range-finding study:</u> 0, 100, 200, 300, 600, 900, 1200 ml/m ³ , 4 h/d; pre- and perinatal ex- aminations for mortal- ity <u>main study:</u> 0, 100 ml/m ³ , 4 h/d; postnatal examinations	at 200 ml/m³ and above: <u>offspring:</u> mortality ↑ (25%) 900 ml/m³: 100% resorption rate 100 ml/m³: <u>dams:</u> slightly prolonged gestation; <u>offspring:</u> impaired performance in a rotarod test and prolonged latency in an open field test (expos. on GDs 7–13), less activity in a running wheel, poorer results in shock avoid- ance conditioning (expos. on GDs 14–20) and neurochemical alterations in the brain on PND 21	Nelson and Brightwell 1984; Nelson et al. 1981

Table 4 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
ingestion			
mouse, CD-1, 20 ♀	GDs 8–14, 0, 800, 1200 mg/kg b.w. and d, exam on PNDs 1, 8, 15, 22	at 800 mg/kg b.w. and above: <u>offspring</u> : litter size ↓, birth weights ↓ and visible tail deformities ↑ 1200 mg/kg b.w.: <u>dams</u> : b.w. gain ↓; <u>offspring</u> : postnatal survival rate ↓	Wier et al. 1987
mouse, CD-1, 50 ♀	GDs 7–14, 0, 3605 mg/kg b.w. and d, postnatal examinations	3605 mg/kg b.w.: <u>dams</u> : 10% mortality; <u>offspring</u> : 100% mortality	Schuler et al. 1984

Key: GD: day of gestation; PND: postnatal day;

SD: Sprague Dawley; n.s.: not specified

Table 5 Studies of prenatal developmental toxicity of EGEEacetate

Species, strain, No. of animals per group	Exposure	Findings	References
inhalation			
rat, F344, 30 ♀	GDs 6–15, 0, 50, 100, 200, 300 ml/ m ³ , 6 h/d, exam on GD 21	50 ml/m³: NOAEC at 100 ml/m³ and above : <u>dams</u> : haematological effects; <u>foetuses</u> : variations ↑ at 200 ml/m³ and above: <u>dams</u> : feed consumption and b.w. gain ↓; <u>foetuses</u> : total resorptions ↑, foetal weight ↓, skeletal malformations (cervical ribs uni- or bilaterally) 300 mg/kg b.w.: <u>foetuses</u> : external, visceral and skeletal malformations	Tyl et al. 1988
rat, SD, 9–20 ♀	GDs 7–15, 0, 130, 390, 600 ml/m ³ , 7 h/d, exam on GD 20	130 ml/m³: <u>foetuses</u> : foetal weight ↓ at 390 ml/m³ and above: <u>foetuses</u> : resorptions ↑, foetal weight ↓, visceral variations (cranial) and malforma- tions (mainly cardiac malformations), skeletal malformations (wavy and fused 14th ribs) and variations (mainly reduced ossification)	Nelson et al. 1984

Table 5 (Continued)

Species, strain, No. of animals per group	Exposure	Findings	References
		600 ml/m³: <u>foetuses</u> : total resorptions; <u>dams</u> : n.s.	
rabbit , Dutch, 23–24 ♀	GDs 6–18 , 0, 25, 100, 400 ml/m ³ , 6 h/d, exam on GD 29	25 ml/m³: NOAEC 100 ml/m³: <u>foetuses</u> : foetal weight ↓, skeletal variations and defects ↑ (no “major”) 400 ml/m³: <u>dams</u> : feed consumption and b.w. gain ↓ and haemoglobin ↓; <u>foetuses</u> : postimplantation losses ↑, external and visceral defects ↑ (“minor”), skeletal variations and defects ↑ (“minor” and “major”)	Johnson 2002; Doe 1984
rabbit , white New Zealand, 24 ♀	GDs 6–18 , 0, 50, 100, 200, 300 ml/m ³ , 6 h/d, exam on GD 29	50 ml/m³: NOAEC at 100 ml/m³ and above: <u>dams</u> : b.w. gain ↓, clinical signs and platelet count ↓; <u>foetuses</u> : foetal weight ↓ and increased incidence of variations (reduced ossification) at 200 ml/m³ and above: <u>foetuses</u> : number of live foetuses ↓, external malformations ↑ (tail malformations), visceral malformations ↑ (heart malformations), skeletal malformations ↑ (14th ribs) and variations ↑	Tyl et al. 1988
ingestion			
mouse , CD-1, 20 ♀ and 20 ♂	multi-generation study , 0, 900, 1800, 3000 mg/kg b.w. and d, drinking water	900 mg/kg b.w.: NOAEL 1800 mg/kg b.w.: testicular atrophy (F ₂ animals) 3000 mg/kg b.w.: number of live offspring/litter ↓ and number of litters/pair ↓	BUA 1995
dermal rat , SD, 17–18 ♀	GDs 7–16 , 0, 6000 mg/kg b.w. and d, exam on GD 21	6000 mg/kg b.w.: <u>dams</u> : b.w. gain ↓; <u>foetuses</u> : total resorptions ↑, number of live foetuses/litter ↑, foetal weight ↓, cardiovascular malformations, skeletal variations and retarded ossifications ↑	Hardin et al. 1984

Key: GD: day of gestation; SD: Sprague Dawley; n.s.: not specified

In a developmental toxicity study relevant for the present assessment that was carried out in groups of 24 Wistar rats and 24 Dutch rabbits with inhalation exposure of the animals to **EGEE** concentrations of 0, 10, 50 and 250 ml/m³ (rats) and 0, 10, 50 and 175 ml/m³ (rabbits) for 6 hours a day from days 6 to 15 (rats) and days 6 to 18 (rabbits) of gestation, the NOAEC for developmental toxicity was 50 ml/m³ for both species (Doe 1984; Table 4). Rats revealed significantly increased incidences of externally visible and visceral anomalies ("minor defects"; 18.4%; control: 11.7%) and of skeletal anomalies ("minor defects"; 97.5%; control: 46.3%) at 250 ml/m³. Malformations ("major defects") were found in only one animal with fusion of the right kidney or ureter with the left kidney and a rudimentary right kidney. Maternal effects with decreases of haemoglobin, haematocrit and mean corpuscular volume of the erythrocytes also only occurred at 250 ml/m³. In rabbits, no maternal effects were observed at 175 ml/m³, but there was an increased incidence of skeletal anomalies ("minor defects"; 64.5%; control: 32.5%) and skeletal variations (79.1%; control: 51.5%) in foetuses (Doe 1984; Table 4).

In a developmental toxicity study carried out with **EGEE** in white New Zealand rabbits with exposure from days 1 to 18 of gestation, an increased incidence of resorptions, malformations and anomalies (*e.g.* ventral wall defects and fusion of aorta with pulmonary artery) and variations (*e.g.* extra ribs and variations of sternbrae) were found in the maternally toxic range with clearly reduced feed consumption, but only slightly reduced body weight gains. The higher concentration of 617 ml/m³ led to maternal mortality and total resorptions (Andrew and Hardin 1984; Table 4).

In prenatal developmental toxicity studies carried out with **EGEE acetate** in F344 rats and white New Zealand rabbits, the NOAEC was also 50 ml/m³. In rats, there was an increased incidence of variations from 100 ml/m³, skeletal malformations (uni- or bilateral cervical ribs) from 200 ml/m³ and externally visible, visceral and skeletal malformations at 300 ml/m³. In rabbits, the incidence of variations (reduced ossification) was increased from 100 ml/m³, and externally visible tail and heart malformations as well as an increased incidence of 14th ribs were even observed from 200 ml/m³ (Tyl et al. 1988; Table 5).

After both ingestion and subcutaneous injection of **EGEE** (see Table 4) to rats for the whole period of gestation, the proportion of foetuses with skeletal aberrations was increased in relation to the dose at 47 mg/kg body weight and day and above (Stenger et al. 1971). Cardiovascular anomalies were observed from 200 mg/kg body weight and day (Goad and Cranmer 1984). A NOAEL of 23 mg/kg body weight and day was found for both ingestion and subcutaneous injection (Stenger et al. 1971). In mice, ingestion of the lowest dose of 1000 mg/kg body weight and day from days 8 to 14 of gestation led to reduced foetal weight, and 1800 mg/kg body weight and day caused an increased incidence of resorptions and malformations (Wier et al. 1987).

The dermal application of **EGEE** at 3445 mg/kg body weight and day and of **EGEE acetate** at 6000 mg/kg body weight from days 7 to 16 of gestation led to foetal mortality, reduced foetal weight, and visceral and skeletal anomalies. Heart

malformations were mainly observed. Lower doses were not used; **EGEE** was lethal for the foetuses at 6889 mg/kg body weight and day. This dose led to ataxia and reduced liver weights in the dams (Hardin et al. 1982, 1984; Table 4 and Table 5).

Postnatal developmental toxicity

When pregnant rats were exposed to **EGEE** by inhalation at 100 ml/m³ from days 7 to 13 or days 14 to 20 of gestation, impaired performance in a rotarod test, prolonged latency in an open field test, less activity in a running wheel, poorer results in shock avoidance conditioning and neurochemical alterations in the brain were found in the pups as compared with the control group (Nelson and Brightwell 1984; Nelson et al. 1981; Table 4). Since only one concentration was used, the relevance of the findings for possible concentration-response relationships cannot be assessed, nor can a final assessment be made.

Offspring of pregnant mice that inhaled **EGEE** at a concentration of 800 ml/m³ from days 8 to 14 of gestation revealed reduced litter sizes and birth weights and visible tail deformities. The postnatal survival rate was decreased at 1200 mg/kg body weight and day (Wier et al. 1987; Table 4).

Genotoxicity

In vitro

EGEE revealed no mutagenicity in *S. typhimurium* or *E. coli* both in the presence and in the absence of metabolic activation. In several sister chromatid and chromosome aberration tests carried out with **EGEE** in CHO cells, increased rates of sister chromatid exchanges and of chromosome aberrations were observed without metabolic activation only from very high concentrations of 3179 µg/ml and 6830 µg/ml, respectively. The clastogenicity in CHO cells was reduced or eliminated when metabolic activation had been added to the in vitro test system. No genotoxicity was observed in an HPRT test in CHO cells, whereas significantly increased mutation rates were obtained at some concentrations in the mouse lymphoma test with metabolic activation (BUA 1995). However, since these could not be reproduced (NTP 1993) and were in the range of the control values of the other test series, this finding is not regarded as relevant for the present assessment. Nor was **EGEE acetate** genotoxic in the *Salmonella* mutagenicity assay, in a test for sister chromatid exchanges in CHO cells or in the HPRT test (ECB 2000 b).

In vivo

In vivo, no genotoxicity was detected with **EGEE** in *Drosophila melanogaster* (SLRL test) or mice (micronucleus test) (BUA 1995).

EGEE acetate was also negative in a micronucleus test in mice (ECB 2000 b).

Carcinogenicity

Groups of 50 male and 50 female F344 rats and B6C3F1 mice were given EGEE by gavage on 5 days per week for 103 weeks at doses of 0, 500, 1000 and 2000 mg/kg body weight and day. Since mortality was markedly increased (mainly because of gastric ulcerations) in rats and mice in the high dose group, all animals of this dose group were sacrificed after 18 weeks. A dose-related reduction of body weight gain was observed in rats of the low and middle dose groups. Gross-pathological examinations revealed enlarged adrenals and testicular atrophy in male rats of the low and middle dose groups. Testicular atrophy was found in male mice from 1000 mg/kg body weight and day (Melnick 1984). Since no comprehensive histopathological examinations were carried out, no conclusions can be drawn with regard to carcinogenicity.

No carcinogenicity studies are available for **2-ethoxyethyl acetate**.

Manifesto (MAK value, classification)

Since EGEE is readily absorbed through the skin and the toxic metabolite ethoxyacetic acid accumulates during the working week, systemic exposure to ethoxyacetic acid is decisive for toxicity and therefore the basis for deriving the MAK value. In 1992, the BAT value for EGEE was established at 50 mg ethoxyacetic acid/l urine (Henschler and Lehnert 1993 a). In 1994, the MAK value for EGEE was established on the basis of the findings obtained by Ratcliffe et al. (1989) since effects on sperm parameters could not be ruled out in the group of workers who excreted 85 ± 31.3 mg 2-ethoxyacetic acid/g creatinine (about 100 mg/l urine). A MAK value of 5 ml/m³ was established assuming that this concentration corresponded to ethoxyacetic acid concentrations of 10 to 35 mg/l in the urine at the end of a working week. However, a new PBPK model shows that the concentration of EGEE of 5 ml/m³ after inhalation exposure alone corresponds to about 120 mg ethoxyacetic acid/l urine (95th percentile) at the end of a working week. Since effects on sperm may occur at about 100 mg ethoxyacetic acid/l urine and the BAT value is 50 mg ethoxyacetic acid/l urine, the MAK value has been lowered to 2 ml/m³; this correlates with the BAT value of 50 mg ethoxyacetic acid/l urine according to the PBPK model. In 2001, Peak Limitation Category II with an excursion factor of 8 was established for EGEE by analogy to other short-chain glycol ethers since the metabolite ethoxyacetic acid responsible for the critical systemic toxicity has a very long half-life and irritation is expected only above 50 ml/m³. This excursion factor has been retained.

EGEE was not mutagenic in vitro, but showed clastogenicity at high concentrations. No genotoxicity was observed in vivo in a micronucleus test in mice. No classification in any of the germ cell mutagen categories is therefore required.

In a carcinogenicity study, rats and mice were exposed for 2 years, and no tumours were observed by gross pathology. Since no comprehensive histopathological

examinations were carried out, no conclusions can be drawn with regard to carcinogenicity. However, there is no evidence to justify a classification of EGEE in one of the Carcinogen Categories.

A NOAEC of 50 ml/m³ was obtained for developmental toxicity in rats and rabbits. Visceral and skeletal defects and variations, and sometimes malformations as well, were observed in rats from 250 ml/m³. The incidence of skeletal defects and variations was increased in Dutch rabbits after 6-hour exposure to EGEE at 175 ml/m³ daily from days 6 to 18 of gestation; an increased incidence of malformations was observed at 160 ml/m³ after 7-hour exposure of white New Zealand rabbits from days 1 to 18 of gestation. Although the MAK value for EGEE has been lowered from 5 to 2 ml/m³, the margin between the NOAEC of 50 ml/m³, or between 160 ml/m³, *i.e.* the concentration which led to an increased incidence of malformations in rabbits, and the MAK value is not high enough for a classification in Pregnancy Risk Group C. Therefore, EGEE remains in pregnancy risk group B. The high absorption of EGEE and EGEE acetate through the skin and the accumulation of ethoxyacetic acid in humans has been taken into account here.

Since EGEE is readily absorbed through the skin, the designation "H" has been retained and is justified.

EGEE showed no sensitizing potential in a maximization test carried out in guinea pigs. No other studies or effects in humans are available. The substance is therefore not designated with "Sa" or "Sh".

References

- Andrew FD, Hardin BD (1984) Developmental effects after inhalation exposure of gravid rabbits and rats to ethylene glycol monoethylether. *Environ Health Perspect* 57: 13–23
- Angerer J, Lichterbeck E, Begerow J, Jekel S, Lehnert G (1990) Occupational chronic exposure to organic solvents. XIII. Glycolether exposure during the production of varnishes. *Int Arch Occup Environ Health* 62: 123–126
- Angerer J, Rüdiger H, Schaller KH, Söhnlein B, Weltle D, Schmidt-Wiederkehr P, Lehnert G (1991) Berufliche Glykoletherexposition – Untersuchungen zu gentoxischen Wirkungen und zur Evaluierung von BAT-Werten (Occupational exposure to glycol ether – studies of genotoxicity and of the evaluation of BAT values) (German). Lecture given at the 31st Annual Meeting of the German Society of Occupational Medicine in Berlin, Mar. 11–14, 1991
- Barbee SJ, Terrill JB, DeSousa DJ, Conaway CC (1984) Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. *Environ Health Perspect* 57: 157–163
- Barber ED, Teetsel NM, Kolberg KF, Guest D (1992) A comparative study of the rates of *in vitro* percutaneous absorption of eight chemicals using rat and human skin. *Fundam Appl Toxicol* 19: 493–497
- BUA (GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance) (1995) Ethyl glycol/ethyl glycol acetate BUA Report 176, Hirzel Wissenschaftliche Verlagsgesellschaft, Stuttgart
- Chen PC, Hsieh GY, Wang JD, Cheng T-J (2002) Prolonged time to pregnancy in female workers exposed to ethylene glycol ethers in semiconductor manufacturing. *Epidemiology* 13: 191–196

- Chester A, Hull J, Andrew F (1986) Lack of teratogenic effect after ethylene glycol monoethyl ether (EGEE) in rats via drinking water. *Teratology* 33: 57C
- Chia S-E, Foo S-C, Khoo NY, Jeyaratnam J (1997) Menstrual patterns of workers exposed to low levels of 2-ethoxyethylacetate (EGEEA). *Am J Ind Med* 31: 148–152
- Cordier S, Bergeret A, Goujard J, Ha MC, Ayme S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R, Candela S, Dale I, Dananche B, de Vigan C, Fevotte J, Kiel G, Mandereau L (1997) Congenital malformation and maternal occupational exposure to glycol ethers. Occupational Exposure and Congenital Malformations Working Group. *Epidemiology* 8: 355–363
- Cordier S, Szabova E, Fevotte J, Bergeret A, Plackova S, Mandereau L (2001) Congenital malformations and maternal exposure to glycol ethers in the Slovak Republic. *Epidemiology* 12: 592–593
- Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Com M (1996) Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *Am J Epidemiol* 143: 707–717
- Doe JE (1984) Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. *Environ Health Perspect* 57: 33–41
- Dugard PH, Walker M, Mawdsley SJ, Scott RC (1984) Absorption of some glycol ethers through human skin *in vitro*. *Environ Health Perspect* 57: 193–197
- ECB (European Chemicals Bureau) (2000 a) 2-Ethoxyethanol. IUCLID dataset, 18.02.2000, ECB, Ispra, Italy
- ECB (European Chemicals Bureau) (2000 b) 2-Ethoxyethyl acetate. IUCLID dataset, 18.02.2000, ECB, Ispra, Italy
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (2005) The toxicology of glycol ethers and its relevance to man (fourth edition). Volume I, II, Technical Report No 95, ECETOC, Brussels, Belgium
- Gargas ML, Tyler TR, Sweeney LM, Corley RA, Weitz KK, Mast TJ, Paustenbach DJ, Hays SM (2000) A toxicokinetic study of inhaled ethylene glycol ethyl ether acetate and validation of a physiologically based pharmacokinetic model for rat and human. *Toxicol Appl Pharmacol* 165: 63–73
- Goad PT, Cranmer JM (1984) Gestation period sensitivity of ethylene glycol monoethyl ether in rats. *Toxicologist* 4: 87
- Gray RH, Correa A, Hakim R, Cohen R, Com M, Shah F, Rothman N, Hou W, Secat H (1996) Ethylene glycol ethers and reproductive health in semiconductor workers. *Occup Hyg* 2: 331–338
- Groeseneken D, Veulemans H, Masschelein R (1986 a) Respiratory uptake and elimination of ethylene glycol monoethyl ether after experimental human exposure. *Br J Ind Med* 43: 544–549
- Groeseneken D, Veulemans H, Masschelein R (1986 b) Urinary excretion of ethoxyacetic acid after experimental human exposure to ethylene glycol monoethyl ether. *Br J Ind Med* 43: 615–619
- Groeseneken D, Veulemans H, Masschelein R, van Vlem E (1987 a) Pulmonary absorption and elimination of ethylene glycol monoethyl ether acetate in man. *Br J Ind Med* 44: 309–316
- Groeseneken D, Veulemans H, Masschelein R, van Vlem E (1987 b) Ethoxyacetic acid: a metabolite of ethylene glycol monoethyl ether acetate in man. *Br J Ind Med* 44: 488–493
- Ha M-C, Cordier S, Dananche B, Bergeret A, Mandereau L, Bruno F (1996) Congenital malformations and occupational exposure to glycol ethers: a European collaborative case-control study. *Occup Hyg* 2: 417–421
- Hardin BD, Niemeier RW, Smith RJ, Kuczuk MH, Mathinos PR, Weaver TF (1982) Teratogenicity of 2-ethoxyethanol by dermal application. *Drug Chem Toxicol* 5: 277–294

- Hardin BD, Goad PT, Burg AR (1984) Developmental toxicity of four glycol ethers applied cutaneously to rats. *Environ Health Perspect* 57: 69–74
- Hays SM, Tyler TR, Snellings WM, Weitz KK, Corley RA, Kirman CR, Gargas ML (1999) Physiologically based pharmacokinetic (PBPK) modelling of ethylene glycol ethers and acetates in pregnant rats. *Toxicologist* 48: 142–143
- Henschler D, Lehnert G (1993 a) 2-Ethoxyethanol. Biologische Arbeitsstoff-Toleranz-Werte (BAT-Werte) und Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA), 6. Lieferung, VCH-Verlag, Weinheim
- Henschler D, Lehnert G (1993 b) 2-Ethoxyethylacetat. Biologische Arbeitsstoff-Toleranz-Werte (BAT-Werte) und Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA), 6. Lieferung, VCH-Verlag, Weinheim
- Horimoto M, Isobe Y, Isogai Y, Tachibana M (2000) Rat epididymal sperm motion changes induced by ethylene glycol monoethyl ether, sulfasalazine, and 2,5-hexandione. *Reprod Toxicol* 14: 55–63
- Hsieh GY, Wang JD, Cheng TJ, Chen PC (2005) Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry. *Occup Environ Med* 62: 510–516
- Isobe Y, Horimoto M, Isogai Y, Shirai N, Tachibana M (1996) Studies on epididymal sperm parameters for detecting effects on male fertility. *Teratology* 54: 40A
- Johanson G, Michel I, Norback D, Nise G, Tillberg A (1989) Biological monitoring of exposure to ethylene glycol ethers. *Arch Toxicol*, Suppl 13: 108–111
- Johnson W (2002) Final report on the safety assessment of ethoxyethanol and ethoxyethanol acetate. *Int J Toxicol* 21, Suppl 1: 9–62
- Kezic S, Mahieu K, Monster AC, de Wolff FA (1997) Dermal absorption of vaporous and liquid 2-methoxyethanol and 2-ethoxyethanol in volunteers. *Occup Environ Med* 54: 38–43
- Kim Y, Lee N, Sakai T, Yang K-S, Park S, Lee CR, Cheong H-K, Moon Y (1999) Evaluation of exposure to ethylene glycol monoethyl ether acetates and their possible haematological effects on shipyard painters. *Occup Environ Med* 56: 378–382
- Lamb JC, Gulati DK, Russell VS, Hommel L, Sabharwal PS (1984) Reproductive toxicity of ethylene glycol monoethyl ether tested by continuous breeding of CD-1 mice. *Environ Health Perspect* 57: 85–90
- Lamb JC, Gulati DK, Russell VS, Hommel L, Poonacha KB (1997) Ethylene glycol monoethyl ether (2-ethoxyethanol). *Environ Health Perspect* 105, Suppl 1: 219–220
- Lamm SH, Kutcher JS, Morris CB (1996) Spontaneous abortions and glycol ethers used in the semiconductor industry: an epidemiologic review. *Occup Hyg* 2: 339–354
- Lockley DJ, Howes D, Williams FM (2002) Percutaneous penetration and metabolism of 2-ethoxyethanol. *Toxicol Appl Pharmacol* 180: 74–82
- Lockley DJ, Howes D, Williams FM (2005) Cutaneous metabolism of glycol ethers. *Arch Toxicol* 79: 160–168
- Loh CH, Shih TS, Liou SH, Lin YC, Hsieh AT, Chen CY, Liao GD (2003) Haematological effects among silk screening workers exposed to 2-ethoxy ethyl acetate. *Occup Environ Med* 60: e7
- Lowry LK, Stump DA, Orbaugh C, Rieders F (1993) Applications of biological monitoring in occupational health practice: practical application of urinary 2-ethoxyacetic acid to assess exposure to 2-ethoxyethyl acetate in large format silk-screening operations. *Int Arch Occup Environ Health* 65, Suppl 1: S47–S51
- Melnick RL (1984) Toxicities of ethylene glycol and ethylene glycol monoethyl ether in Fischer 344/N rats and B6C3F1 mice. *Environ Health Perspect* 57: 147–155

- Nagano K, Nakayama E, Koyano M, Oobayashi H, Adachi H, Yamada T (1979) Testicular atrophy of mice induced by ethylene glycol mono alkyl ethers (jpn). *Sangyo Igaku* 21: 29–35
- Nelson BK, Brightwell WS (1984) Behavioral teratology of ethylene glycol monomethyl and monoethyl ethers. *Environ Health Perspect* 57: 43–46
- Nelson BK, Brightwell WS, Setzer JV, Taylor BJ, Hornung RW, O'Donohue TL (1981) Ethoxyethanol behavioural teratology in rats. *Neurotoxicology* 2: 231–249
- Nelson BK, Setzer JV, Brightwell WS, Mathinos PR, Kuczuk MH, Weaver TE, Goad PT (1984) Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environ Health Perspect* 57: 261–271
- NTP (National Toxicology Program) (1993) Technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol administered by drinking water to F344/N rats and B6C3F1 mice. NTP Technical Report Series No. NIH/PUB-93-3349, NIH/TOX-26, US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, USA
- Ratcliffe JM, Schrader SM, Clapp DE, Halperin WE, Turner TW, Hornung RW (1989) Semen quality in workers exposed to 2-ethoxyethanol. *Br J Ind Med* 46: 399–406
- Schenker MB (1996) Reproductive health effects of glycol ether exposure in the semiconductor industry. *Occup Hyg* 2: 367–372
- Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, Samuels SJ, Saiki CL, Swan SH (1995) Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *Am J Ind Med* 28: 639–659
- Schrader SM, Turner TW, Ratcliffe JM, Welch LS, Simon SD (1996) Combining reproductive studies of men exposed to 2-ethoxyethanol to increase statistical power. *Occup Hyg* 2: 411–415
- Schuler RL, Hardin BD, Niemeier RW, Booth G, Hazelden K, Piccirillo V, Smith K (1984) Results of testing fifteen glycol ethers in a short-term *in vivo* reproductive toxicity assay. *Environ Health Perspect* 57: 141–146
- Shaw GM, Velie EM, Katz EA, Morland KB, Schaffer DM, Nelson V (1999) Maternal occupational and hobby chemical exposures as risk factors for neural tube defects. *Epidemiology* 10: 124–129, Erratum *Epidemiology* 10: 777
- Smyth HF, Carpenter CP, Weil CS (1951) Range-finding toxicity data: list IV. *Arch Ind Hyg Occup Med* 4: 119–122
- Söhnlein B, Letzel S, Weltle D, Rüdiger HW, Angerer J (1993) Occupational chronic exposure to organic solvents. XIV Examinations concerning the evaluation of a limit value for 2-ethoxyethanol and 2-ethoxyethyl acetate and the genotoxic effects of these glycol ethers. *Int Arch Occup Environ Health* 64: 479–484
- Stenger E-G, Aepli L, Müller D, Penheim E, Thomann P (1971) Zur Toxikologie des Äthylen-glykol-Monoäthyläthers (Toxicology of ethylene glycol monoethyl ether) (German). *Arzneim-Forsch* 21: 880–885
- Swan SH, Forest W (1996) Reproductive risks of glycol ethers and other agents used in semiconductor manufacturing. *Occup Hyg* 2: 373–385
- Swan SH, Beaumont JJ, Hammond SK, Von Behren J, Green RS, Hallock MF, Woskie SR, Hines CJ, Schenker MB (1995) Historical cohort study of spontaneous abortion among fabrication workers in the semiconductor health study: agent-level analysis. *Am J Ind Med* 28: 751–769
- Sweeney LM, Tyler TR, Kirman CR, Corley RA, Reitz RH, Paustenbach DJ, Holson JF, Whorton MD, Thompson KM, Gargas ML (2001) Proposed occupational exposure limits for select ethylene glycol ethers using PBPK models and Monte Carlo simulations. *Toxicol Sci* 62: 124–139

- Truchon G, Tardif R, Droz PO, Charest-Tardif G, Pierrehumbert G (2006) Biological exposure indicators: quantification of biological variability using toxicokinetic modeling. *J Occup Environ Hyg* 3: 137–143
- Truhaut R, Dutestre-Catella H, Ngyen PL, Vu NH (1979) Comparative toxicological study of ethyl glycol acetate and butyl glycol acetate. *Toxicol Appl Pharmacol* 51: 117–127
- Tyl RW, Pritts IM, France KA, Fisher LC, Tyler TR (1988) Developmental toxicity evaluation of inhaled 2-ethoxyethanol acetate in Fischer 344 rats and New Zealand white rabbits. *Fundam Appl Toxicol* 10: 20–39
- Veulemans H, Groeseneken D, Masschelein R, Van Vlem E (1987) Field study of the urinary excretion of ethoxyacetic acid during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate. *Scand J Work Environ Health* 13: 239–242
- Veulemans H, Steeno O, Masschelein R, Groeseneken D (1993) Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case-control study. *Br J Ind Med* 50: 71–78
- Wang RS, Suda M, Gao X, Wang BL, Honma T (2003) Effects of 2-ethoxyethanol on spermatogenesis in the exposed workers. *Toxicol Lett* 144: S111
- Wang RS, Suda M, Gao X, Wang BL, Nakajima T, Honma T (2004 a) Health effects of exposure to ethylene glycol monoethyl ether in female workers. *Ind Health* 42: 447–451
- Wang RS, Suda M, Gao X, Wang BL, Honma T (2004 b) Effect of ALDH2 gene polymorphism on the metabolism and toxicity of 2-ethoxyethanol in the exposed workers. *Toxicologist* 78: 423–424
- Wang RS, Ohtani K, Suda M, Nakajima T (2006) Inhibitory effect of ethylene glycol monoethyl ether on rat sperm motion. *Ind Health* 44: 665–668
- Welch LS, Cullen MR (1988) Effect of exposure to ethylene glycol ethers on shipyard painters: III. Hematologic effects. *Am J Ind Med* 14: 527–536
- Welch LS, Schrader SM, Turner TW, Cullen MR (1988) Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. *Am J Ind Med* 14: 509–526
- Wier PJ, Lewis SC, Traul KA (1987) A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. *Teratogen Carcinogen Mutagen* 7: 55–64
- Wilkinson SC, Williams FM (2002) Effects of experimental conditions on absorption of glycol ethers through human skin *in vitro*. *Int Arch Occup Environ Health* 75: 519–527
- Yoon CY, Hong CM, Song JY, Cho YY, Choi KS, Lee BJ, Kim CK (2001) Effect of ethylene glycol monoethyl ether on the spermatogenesis in pubertal and adult rats. *J Vet Sci* 2: 47–51
- Yoon CY, Hong CM, Cho YY, Chung YH, Min HK, Yun YW, Lee BJ, Yang KH, Lee YS, Kim CK (2003) Flow cytometric assessment of ethylene glycol monoethyl ether on spermatogenesis in rats. *J Vet Med Sci* 65: 207–212

completed 14.12.2006