



**Substance Name(s): 2-Ethoxyethanol**

**EC number: 203-804-1**

**CAS Number: 110-80-5**

**MEMBER STATE COMMITTEE  
SUPPORT DOCUMENT FOR IDENTIFICATION OF**

**2-ETHOXYETHANOL**

**AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF  
ITS CMR PROPERTIES**

**Adopted on 25 November 2010**

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## LIST OF ABBREVIATIONS

|               |   |
|---------------|---|
| <b>CMR</b>    | <b>Carcinogenic, Mutagenic or toxic to Reproduction</b> |
| <b>EGEE</b>   | <b>2-Ethoxyethanol</b>                                  |
| <b>EGME</b>   | <b>2-Methoxyethanol</b>                                 |
| <b>EU RAR</b> | <b>European Union Risk Assessment Report</b>            |
| <b>PBT</b>    | <b>Persistent, Bioaccumulative and Toxic</b>            |
| <b>SVHC</b>   | <b>Substance of Very High Concern</b>                   |
| <b>vPvB</b>   | <b>Very Persistent and very Bioaccumulative</b>         |

**Substance Name(s):** 2-Ethoxyethanol (ethylene glycol monoethyl ether; EGEE)

**EC Number(s):** 203-804-1

**CAS number(s):** 110-80-5

- *2-Ethoxyethanol* is identified as a substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction 1B.

**Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance giving rise to an equivalent level of concern**

2-Ethoxyethanol (EGEE) is listed under index number 603-012-00-X in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as toxic to reproduction, category 2<sup>1</sup>.

Therefore, this classification of the substance(s) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

**Registration number(s) of the substance or of substances containing a given constituent/impurity or leading to the same transformation or degradation products:**

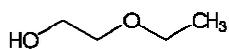
Not relevant.

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<sup>1</sup> This corresponds to a classification as toxic for reproduction (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances)

**PART I****JUSTIFICATION****1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES****1.1 Name and other identifiers of the substance****Table 1: Substance identity**

|   |   |
|---|---|
| <b>EC number:</b>                                     | 203-804-1                                     |
| <b>EC name:</b>                                       | 2-Ethoxyethanol                               |
| <b>CAS number (in the EC inventory):</b>              | 110-80-5                                      |
| <b>CAS number:</b>                                    | 110-80-5                                      |
| <b>CAS name:</b>                                      | Ethanol, 2-ethoxy-                            |
| <b>IUPAC name:</b>                                    | 2-Ethoxyethanol                               |
| <b>Index number in Annex VI of the CLP Regulation</b> | 603-012-00-X                                  |
| <b>Molecular formula:</b>                             | C <sub>4</sub> H <sub>10</sub> O <sub>2</sub> |
| <b>Molecular weight range:</b>                        | 90.1 g/mol                                    |
| <b>Synonyms:</b>                                      | Ethylene glycol monoethyl ether; EGEE         |

**Structural formula:****1.2 Composition of the substance****Name:** 2-Ethoxyethanol**Description:****Degree of purity:** > 99 % w/w

**Table 2: Constituents**

| Constituents                        | Typical concentration | Concentration range | Remarks |
|-------------------------------------|-----------------------|---------------------|---------|
| 2-Ethoxyethanol<br>EC No: 203-804-1 | > 99 % w/w            |                     |         |

**Table 3: Impurities**

| Impurities                       | Typical concentration | Concentration range | Remarks |
|----------------------------------|-----------------------|---------------------|---------|
| unknown impurities               | < 1 % w/w             |                     |         |
| acetic acid;<br>EC No: 200-580-7 | < 0.005 % w/w         |                     |         |

### 1.3 Physico-chemical properties

**Table 4: Overview of physicochemical properties**

| Property  | Value   | References               |
|---|---|--------------------------|
| Physical state at 20°C and 101.3 kPa              | Colourless liquid                             |                          |
| Melting/freezing point                            | < - 80 °C                                     | Ullmann, 1978            |
| Boiling point                                     | 132 - 137 °C at 1013hPa                       | Ullmann, 1978            |
| Vapour pressure                                   | 5.3 hPa at 20 °C                              | Kirk-Othmer, 1980        |
| Water solubility                                  | miscible in each ratio at 20 °C               | Kirk-Othmer, 1980        |
| Partition coefficient n-octanol/water (log value) | log Pow -0.54 to -0.10 <sup>1)</sup>          | Dearden & Bresnen, 1988  |
| Dissociation constant                             |   |                          |
| Relative density                                  | 0.930 at 20 °C                                | Ullmann, 1978            |
| Surface tension                                   | 69.5 mN/m at 25 °C <sup>2)</sup>              | Union Carbide, 1998      |
| Flash point                                       | 40 °C (closed cup)                            | Chemsafe, 1996           |
| Flammability                                      | flammable <sup>3)</sup>                       | Chemsafe, 1996           |
| Ignition temperature                              | 235 °C  | Chemsafe, 1996           |
| Explosive properties                              | not explosive <sup>4)</sup>                   | Chemsafe, 1996           |
| Oxidising properties                              | no oxidising properties <sup>5)</sup>         | Chemsafe, 1996           |
| Henry's law constant                              | 0.003 Pa * m <sup>3</sup> * mol <sup>-1</sup> | Howard, Meylan; SRC 1993 |

1) a log Pow of - 0.43 was used in the EU RAR draft, 2008

2) Ring method

3) Test A.10 not conducted (substance is a liquid) Test A.12 and A.13 not conducted because of structural reasons

4) No test conducted because of structural reasons

5) No test conducted because of structural reasons

## 2 HARMONISED CLASSIFICATION AND LABELLING

2-Ethoxyethanol is classified and labelled according to Annex VI of Reg. (EC) No 1272/2008, Annex VI, Table 3.1. as follows:

*Index Number:* 603-012-00-X

*Hazard class and category codes*

Flam. Liq. 3

Repr. 1B

Acute Tox. 4 \*<sup>2</sup>

Acute Tox. 4 \*

Acute Tox. 4 \*

*Hazard statement codes*

H226

H360-FD

H332

H312

H302

*Pictogram, signal word codes*

GHS02

GHS08

GHS07

Dgr

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<sup>2</sup> Minimum classification for a category is indicated by the reference \* in the column 'Classification' in Table 3.1.

For certain hazard classes, including acute toxicity and STOT repeated exposure; the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification. This classification shall be applied if none of the following conditions are fulfilled:

— the manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied;

— the minimum classification can be further refined based on the translation table in Annex VII when the physical state of the substance used in the acute inhalation toxicity test is known to the manufacturer or importer. The classification as obtained from Annex VII shall then substitute the minimum classification indicated in this Annex if it differs from it.

*Hazard statement codes*

H226

H360FD

H332

H312

H302

*Specific Conc. Limits; M-factors; Notes: none*

Classification and Labelling of EGEE according to Reg. (EC) No 1272/2008, Annex VI, Table 3.2:

Index Number: 603-012-00-X

*Classification*

R10

Repr. Cat. 2; R60-61

Xn; R20/21/22

*Labelling*

T

R: 60-61-10-20/21/22

S: 53-45

EGEE is included in a list of substances with harmonised classifications already agreed by the Technical Committee for Classification and Labelling but not included in Annex VI of Regulation (EC) No 1272/2008<sup>3</sup>:

R10

Repr. Cat. 2; R60-61

Xn; R20/22

*(deletion of R21)*

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<sup>3</sup> RAC/07/2009/40: Seventh Meeting of the Risk Assessment Committee, 30 June - 3 July 2009, Helsinki, Finland

### **3 ENVIRONMENTAL FATE PROPERTIES**

Not relevant for this type of dossier.

### **4 HUMAN HEALTH HAZARD ASSESSMENT**

#### **4.1 Toxicity for reproduction**

On the summary and discussion of reproductive toxicity according to the EU RAR draft, 2008 see Annex.

### **5 ENVIRONMENTAL HAZARD ASSESSMENT**

Not relevant for this type of dossier.

### **6 CONCLUSIONS ON THE SVHC PROPERTIES**

#### **6.1 CMR assessment**

2-Ethoxyethanol (EGEE) is listed as entry 603-012-00-X in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as toxic to reproduction, category 2. This corresponds to a classification as toxic for reproduction (1B) in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances).

Therefore, this classification of the substance(s) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

## 7 REFERENCES

### Notice:

No re-evaluation was conducted of those references which are cited in this support document and which were taken from the Risk Assessment Report for 2-ethoxyethanol (EU RAR draft, 2008). For the present support document no comprehensive literature survey was carried out, but focus was given to exposure related data.

2-Ethoxyethanol was prioritised under the Existing Substance Regulation (ESR) (Regulation (EEC) No793/93), however, the risk evaluation and/or risk management work for this substance was not finalised by 1 June 2008 (i.e. the date the ESR regulation was repealed and replaced by the REACH Regulation). As rapporteur of this substance according to the ESR, Germany was required to develop an Annex XV transitional report for this substance. This report contains information on hazard and risk documented in an annexed risk assessment report (RAR) following the structure used under the ESR. It also provides information on what possible actions the submitting Member State considers to be necessary in order to reduce the risks identified in the RAR. The Annex XV transitional report has been submitted to ECHA according to the REACH Regulation (EC) No 1907/2006, Article 136(3).

Barbee SJ, Terrill JB, DeSousa DJ, Conaway CC (1984): Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. *Environmental Health Perspectives* 57: 157-163.

Bio/dynamics Inc. (1983): A 13-week inhalation toxicity study of ethylene glycol monoethyl ether in the rabbit. East Millstone, NJ 08873, unpublished data, Project No. 82-7589, October 24, 1983

Chemsafe (1996): National database for safety data of the Physikalisch-technische Bundesanstalt Braunschweig, established by expert judgement.

Cordier S, Bergeret A, Goujard J, Ha M-C, Ayme S, Bianchi F, Calzolari E, De Walle HEK, Knill-Jones R, Candela S, Dale I, Danache B, de Vigan C, Fevotte J, Kiel G, Mandereau L (1997): Congenital malformations and maternal occupational exposure to glycol ethers. *Epidemiology* 8: 355-363.

Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Corn M (1996): Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *American Journal of Epidemiology* 47: 707-717.

Dearden & Bresnen (1988): The measurement of partition coefficients. *Quat. Struct.-Act. Relat.* 7, 133-144.

Doe JE (1984b): Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. *Environ Health Perspect* 57: 33-41.

EU RAR draft, 2008: Risk assessment 2-Ethoxyethanol. Draft of 21.11.2008. Rapporteur Germany, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). [http://echa.europa.eu/doc/trd\\_substances/2\\_ethoxyethanol/rar/trd\\_rar\\_germany\\_ethoxyethanol.pdf](http://echa.europa.eu/doc/trd_substances/2_ethoxyethanol/rar/trd_rar_germany_ethoxyethanol.pdf)

Howard et al. (1993): Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume IV, Solvents 2, Lewis Publishers, Michigan, USA, pp. 280 - 287

Kirk-Othmer (1980): Encyclopedia of chemical technology, 3 rd ed., vol 11; John Wiley & Sons, Inc. 1980.

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.

National Toxicology Program (NTP) (1993): Technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-Butoxyethanol (CAS Nos. 109-86-4, 110-80-5, 111-76-2) administered by drinking water to F344/N rats and B6C3F1 mice, 1-122, Appendices A-G. Report Nos: NIH/PUB-93-3349, NIH/TOX-26. NTIS/PB 94-118106, US Department of Commerce, National Technical Information Service (NTIS).

Ratcliffe JM, Schrader SM, Clapp DE, Halperin WE, Turner TW, Hornung RW (1989): Semen quality in workers exposed to 2-ethoxyethanol. Brit J Indust Med 46: 399-406

Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Jasley BL, McCurdy SA, Samuels SJ, Saiki CL, Swan SH (1995): Association of Spontaneous Abortion and Other Reproductive Effects With Work in the Semiconductor Industry. American Journal of Industrial Medicine 28: 639-659

Stenger EG, Aeppli L, Müller D, Peheim E, Thomann P (1971): Zur Toxikologie des Äthylenglykol-Monoäthyläthers. Arzneimittel-Forschung (Drug Research) 6: 880-885.

Tinston DJ, Doe JE, Godley MJ, Head LK, Killic M, Litchfield MH, Wickramaratne GA (1983a): Ethylene glycol monoethyl ether (EE): Teratogenicity study in rats; ICI Central Toxicology Laboratory, Report No: CTL/P/761, 2-30.

Ullmann (1978): Enzyklopädie der technischen Chemie, 4th ed. Vol.16; Verlag Chemie Weinheim, 1978.

Union Carbide (1998): Surface Tension Measurements of Aqueous Solutions of CELLOSOLVE®-Solvent and CELLOSOLVE®-Acetate. Unpublished test report from September 22, 1998.

Veulemans H, Steeno O, Masschelein R, Groeseneken D (1993): Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case-control study. Brit J Indust Med 50: 71-78.

Welch LS, Cullen MR (1988): Effect of exposure to ethylene glycol ethers on shipyard painters. III. Hematological effects. Am J Ind Med 14: 527-536

## 8 ANNEX

### Summary and discussion of reproductive toxicity according to EU RAR draft, 2008

#### Animal data

Several studies in mice and rats demonstrate adverse effects of 2-ethoxyethanol on the male reproductive system via different exposure routes. The effects reported include: reduction of testes weight and testicular atrophy, degeneration of testes, testicular edema, reduction of sperm count and motility, abnormal sperm morphology and spermatocyte degeneration and absence of more mature sperm cells. It is documented that EGEE adversely affected reproductive performance in mice of both sexes for at least one generation. A NOAEL fertility was derived from the study in CD1 mice of Lamb et al. (1984) of 800 mg/kg bw/day whereas it is stated in the EU RAR draft, 2008 that various other studies show spermatotoxicity at clearly lower doses.

Male reproductive organ toxicity/spermatotoxicity effects were reported in various repeated dose toxicity studies with different species.

It was also clearly shown that 2-ethoxyethanol adversely affects embryonic and fetal development in dose dependent manner. Increasing embryo-/fetomortality, fetal growth retardation and visceral /skeletal malformations and variations were reported at concentrations devoid of maternal toxicity. Table 31 summarises the effects of 2-ethoxyethanol on the reproductive system.

**Table 5: Compilation of NOAELs derived from animal studies related to reproductive toxicity**

| Endpoint                               | species | NOAEL /NOAEC<br>( route of exposure )              | study type   | Reference<br>(in EU RAR draft,<br>2008)        |
|--|---------|--|--|--|
| Fertility                              | mouse   | 800 mg/kg<br>(oral, drinking water)                | fertility study<br>exposure in pre mating<br>period (7 days) | Lamb et al. 1984                               |
| Male<br>reproductive<br>organ toxicity | rabbit  | 100 ppm<br>(390mg/m <sup>3</sup> )<br>(inhalatory) | repeated dose toxicity<br>(13 weeks)                         | Biodynamis Inc<br>1983, Barbee et al.<br>1984, |
| Male<br>reproductive<br>organ toxicity | rat     | 1250 ppm<br>(109 mg/kg bw/day)<br>(oral)           | repeated dose toxicity<br>(13 weeks)                         | NTP, 1993                                      |
| Male<br>reproductive<br>organ toxicity | dog     | 200 µL/kg bw/day<br>(93 mg/kg/d)<br>(oral)         | repeated dose toxicity<br>(13 weeks)                         | Stenger et al. 1971                            |
| Developmental<br>Toxicity              | rat     | 10 ppm (39mg/m <sup>3</sup> )<br>(inhalatory)      | 6h/day on g.d.* 6-15,<br>Dev-Tox. study                      | Doe 1984 b<br>Tinston 1983 a                   |
| Developmental<br>Toxicity              | rat     | 23 mg/kg bw (oral)                                 | 6h/day on g.d.*1-21<br>Dev-Tox. Study                        | Stenger et al. 1971                            |

g.d.: gestational day

**Conclusion:**

Based on available animal data 2-ethoxyethanol is confirmed as reproductive toxicant and classified and labelled for its effects on fertility and development as Repr. Cat. 2; R 60/R61; and Repr. Cat 1b according to the CLP-Regulation respectively.

**Human Data**

The possible associations between exposure to glycol ethers and reproductive disorders were first investigated in a case control study (1019 cases, 475 controls) by Veulemans 1993. Exposure to EGEE was assessed by the presence of the urinary metabolites. Ethoxy acetic acid (EAA). EAA was detected in 39 patients and six controls, with a highly significant odds ratio of 3.11 (p=0,004). A high association of the occupational high exposure group with complete azoospermia and severe oligozoospermia was found. The association between urinary EAA and diagnosis remained significant taking into account possible confounders (other industrial spermatotoxic chemicals).

Further studies supported these findings. Table 32 summarises the findings of epidemiological studies on workers exposed to 2-ethoxyethanol.

**Table 6: Human studies dealing with occupational exposure to EGEE**

| <b>Study population</b>                                       | <b>Study design</b>   | <b>Effects and findings</b>  | <b>Reference (in EU RAR draft, 2008)</b> |
|---|---|--|--|
| Occupational exposure with paint products                     | Case – Control study (1019 : 475) (infertile vs. fertile) Investigation of metabolite in urine (etoxyacetic acid EAA) | Highly significant assoc. OR: 3.11 (p=0,004), of EAA positive subjects had been occupationally exposed; association with azoospermia and severe oligozoospermia                                      | Veulemans, 1993                          |
| 73 ship yard painters and 40 controls (non exposed employees) | Cross sectional study, 8-hour time weighted investigation of workplace air (EGEE, EGME)                               | Proportion of exposed men with oligospermia was 13% versus 5% (controls), proportion of painters with azoospermia was 5% (1% expected) versus 0% OR: 2.8 for oligospermia among non-smoking painters | Welch et al. 1988                        |
| Metal casting process workers in Portland, Oregon             | Cross sectional study, investigation of workplace air conc. Monitoring EEA in urine 27 exposed: 39 non-exposed        | Average sperm count per ejaculate (p.e.) among exposed workers was significantly lower than of controls (113x10 <sup>6</sup> versus 154x10 <sup>6</sup> p.e.)  | Ratcliffe et al.1989                     |

|   |   |   |                      |
|---|---|---|----------------------|
| Fabrication room work in silicon-based semiconductor industry (14 US-companies) | Historical and retrospective nation-wide study  | Investigation of increased abortion rate and subfertility:<br>Small increase of risk of spontaneous abortion in fab room workers (historical:OR: 1.43, 95% CI: 0.95-2.09); prospective: OR: 1.25, 95% CI: 0.65-1.76);<br>No significant decrease in fertility, but reduced fecundability was suggested for some wives of fab workers.                     | Schenker et al. 1995 |
| 2 semiconductor plants (eastern USA)  | Retrospective cohort study (1980 -1987), 1150 pregnancies (561 female employees, 589 wives to male)             | Investigation of increased abortion rate and subfertility:<br>Higher risk of spontaneous abortion in female workers (OR: 2.8, 95% CI: 1.4-5.6) and subfertility (high exposure group: OR: 4.6, 95% CI:1,6 -13.3)<br>In wives of male employees nonsignificant increased risk of subfertility in high exposure group was reported: OR: 1.7, 95%CI:0.7-4.3) | Correa et al.1996    |
| Multicenter study in six regions in Europe                                      | Case-Control 984 cases of major congenital malformations and 11134 controls matched for place and date of birth | Risk of congenital malformations related to glycol ether exposure during pregnancy<br>Congenital malformation associated with glycol ether exposure : 1.44, 95%CI:1,10 -1,90<br>Association appeared particularly strong for neural tube defects, cleft lip and multiple anomalies  | Cordier et al. 1997  |

OR: Odds ratio; CI: Confidence Interval

### Conclusion:

Findings from several epidemiological studies indicate an association between occupational exposure to 2-ethoxyethanol (mostly monitored as EAA in urine) and impairment of reproduction in men and women. Whereas in men spermatotoxic effects (azoospermia, oligospermia) were reported, a higher risk in spontaneous abortions was reported in women.

Congenital malformations in humans such as neural tube defects, cleft lip and multiple anomalies were also associated with glycol ether exposure.

According to the EU RAR draft, 2008 the plausibility of the observations from epidemiology is supported by the data of numerous experimental studies, which demonstrated similar effects in laboratory animals.