9 December 2011

**Substance name: bis(2-methoxyethyl) ether (Diglyme)**
**EC number: 203-924-4**
**CAS number: 111-96-6**

# SUPPORT DOCUMENT FOR IDENTIFICATION OF

# BIS(2-METHOXYETHYL) ETHER (DIGLYME)

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

# NOTE

During the public consultation, in accordance with Article 59 (4) of the REACH Regulation, on the proposed identification of “bis(2-methoxyethyl)ether” as a Substance of Very High Concern (SVHC) on the basis of its classification as toxic for reproduction category 1B no comments were received objecting the conclusion that the substance meets criteria set out in Article 57(c). Therefore, in accordance with Article 59 (6), “bis(2-methoxyethyl)ether” has been included in the Candidate List by ECHA.

The present support document comprises Part I (Justification) of the Annex XV dossier for identification of “bis(2-methoxyethyl)ether” as SVHC on the basis of Article 57(c) of REACH.

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# ABBREVIATIONS

| | |
|---|---|
| CAS | Chemical Abstracts Service |
| CLP | Classification, Labelling and Packaging |
| CMR | Carcinogenic, Mutagenic and toxic to Reproduction |
| CSR | Chemical Safety Report |
| DEGDME | Diethylene glycol dimethyl ether (Diglyme) |
| EC | European Community |
| ECHA | European Chemicals Agency |
| ECETOC | European Centre for Ecotoxicology and Toxicology of Chemicals |
| EEC | European Economic Community |
| EGME | Ethylene glycol monomethyl ether |
| LOAEL | Lowest Observed Adverse Effect Level |
| MAA | Methoxyacetic acid |
| NOAEL | No Observed Adverse Effect Level |
| PBT | Persistent, Bioaccumulative and Toxic |
| SVHC | Substance of Very High Concern |
| US EPA | U.S. Environmental Protection Agency |
| vPvB | Very Persistent and very Bioaccumulative |
| WHO | World Health Organization |

**Substance Name(s): bis(2-methoxyethyl)ether (Diglyme, DEGDME)**

**EC Number(s): 203-924-4**

**CAS number(s):** 111-96-6

- The substance 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(s) meet(s) the CMR (Cat 1 or 2) criteria:**

Bis(2-methoxyethyl)ether (diglyme) is listed as entry 603-139-00-0 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[1] as Repr. 1B, H360FD (May damage fertility. May damage the unborn child.) This corresponds to a classification as toxic to reproduction Repr. Cat. 2; R60-61 ("May impair fertility; May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC).

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 dossiers submitted for the substance?** Yes

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

# JUSTIFICATION

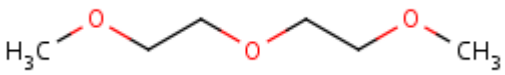
## 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

### 1.1 Name and other identifiers of the substance

**Table 1: Substance identity**

| | |
|---|---|
| **EC number:** | 203-924-4 |
| **EC name:** | Bis(2-methoxyethyl)ether |
| **CAS number (in the EC inventory):** | 111-96-6 |
| **CAS number:** | 111-96-6 |
| **CAS name:** | Ethane, 1,1'-oxybis[2-methoxy- |
| **IUPAC name:** | 1-methoxy-2-(2-methoxyethoxy)ethane |
| **Index number in Annex VI of the CLP Regulation** | 603-139-00-0 |
| **Molecular formula:** | $C_6H_{14}O_3$ |
| **Molecular weight range:** | 134.17g/mol |
| **Synonyms:** | Diglyme<br>DEGDME<br>Diethylenglycoldimethylether<br>Dimethyldiglycol<br>2-(2-Methoxyethoxy)-1-methoxyethane<br>2,5,8-Trioxanonane<br>Di(2-Methoxyethyl) ether<br>Dimethyl carbitol<br>Ether, bis(2-methoxyethyl)<br>1,1'-Oxybis[2-methoxyethane]<br>Methyldiglyme<br>(CAS registry numbers still in use: 70-992-86-8, 54631-70-8, 142939-39-7 although deleted in CAS registry) |

**Structural formula:**



## 1.2 Composition of the substance

**Name:** bis(2-methoxyethyl)ether

**Description:** -

**Degree of purity:** > 80% (m/m)

**Table 2: Constituents**

| Constituents | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| bis(2-methoxyethyl)ether<br>EC-No 203-924-4 | > 80% m/m | | |

**Table 3: Impurities**

| Impurities | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| *Confidential information* | | | |

Purity according to website information from Clariant GmbH[2]: ≥99%.

[2]http://www.clariant.de/C12575E4001FB2B8/vwLookupDownloads/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf/$FILE/2000_SpecialSolvents_Newsroom_Brochures_GlymesBrochure.pdf

## 1.3 Physico-chemical properties

**Table 4: Overview of physico-chemical properties**

| Property | Value | Remarks |
|---|---|---|
| Physical state at 20°C and 101.3 kPa | *Clear liquid with a pleasant odor* | *from registration** |
| Melting/freezing point | *-68°C* | *from registration* |
| Boiling point | *162°C at 1013 hPa* | *from registration* |
| Vapour pressure | *0.6 hPa at 20°C ** | *from registration* |
| Water solubility | *Miscible at each ratio*<br>*pH=7 at 20°C*<br>*940 g/l at 20°C* | *from registration* |
| Partition coefficient n-octanol/water (log $P_{OW}$) | *-0.36 at 25°C* | *Funasaki, 1984* |
| Flashpoint | *59°C at 102.1 kPa* | *from registration* |
| Auto Flammability at 1013hPa | *190°C* | *from registration* |
| Reactivity | *Oxidizes readily in air to form unstable peroxides that may explode spontaneously.* | *Chemical Book*[3] |
| Density | *0.943 – 0.945g/cm³ at 20°C* | *from registration* |

*From dissemination database according to Regulation (EC) No.1907/2006, article 119

Conversion factors (20°C, 1014hPa) (Ecetoc, 2005): 1mg/m³ = 0.179ppm

1ppm = 5.579mg/m³

[3] http://www.chemicalbook.com/Search_EN.aspx?keyword=111-96-6

# 2 HARMONISED CLASSIFICATION AND LABELLING

Bis(2-methoxyethyl)ether is covered by index number 603-139-00-0 in Annex VI, part 3 of Reg. (EC) No 1272/2008 (CLP regulation) as follows:

**Table 5: Classification according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008:**

| Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Spec. Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Hazard Class and Category Code(s) | Hazard statement code(s) | Pictogram, Signal Word Code(s) | Hazard statement code(s) | Suppl. Hazard statement code(s) | | |
| 603-139-00-0 | bis(2-methoxyethyl) ether | 203-924-4 | 111-96-6 | Flam. Liq. 3<br>Repr. 1B | H226<br>H360-FD | GHS02<br>GHS08<br>Dgr | H226<br>H360FD | EUH019 | | |

**Table 6: Classification according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008:**

| Index No | International Chemical Identification | EC No | CAS No | Classification | Labelling | Concentration Limits | Notes |
|---|---|---|---|---|---|---|---|
| 603-139-00-0 | bis(2-methoxyethyl) ether | 203-924-4 | 111-96-6 | R10<br>R19<br>Repr. Cat. 2;<br>R60-61 | T<br>R: 60-61-10-19<br>S: 53-45 | | |

# 3 ENVIRONMENTAL FATE PROPERTIES

*Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).*

# 4 HUMAN HEALTH HAZARD ASSESSMENT

*Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).*

# 5 ENVIRONMENTAL HAZARD ASSESSMENT

*Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).*

# 6 CONCLUSIONS ON THE SVHC PROPERTIES

## 6.1 PBT, vPvB assessment

Not relevant

## 6.2 CMR assessment

Bis(2-methoxyethyl)ether (diglyme) is listed as entry 603-139-00-0 in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/20084 as Repr. 1B, H360FD (May damage fertility. May damage the unborn child.) . This corresponds to a classification as toxic to reproduction Repr. Cat. 2; R60-61 ("May impair fertility; May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC)

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.

## 6.3 Substances of equivalent level of concern assessment

Not relevant.

[4] Regulation (Ec) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

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# ANNEX I

# SUPPLEMENTARY INFORMATION ON TOXICOKINETICS, TOXICITY FOR REPRODUCTION AND NON-CLASSIFICATION FOR THE ENVIRONMENT

## 8 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Diglyme is readily absorbed by oral, dermal and inhalation route of exposure (low molecular weight, excellent solvating properties, logPow, see section 1.3 physico-chemical properties). Diglyme is rapidly and completely absorbed from the gastrointestinal tract (US EPA, 2003). Dermal absorption of glycol ether liquids or vapours is very high. With a permeability constant of $1x10^{-3}$cm/h and a lag time of approximately half an hour diglyme is among the glycol ethers with the highest percutaneous absorption rates (Larese Filon et al, 1999; WHO, 2002).

Glycol ethers in general are readily distributed throughout the body and eliminated through the urine. No substantial accumulation of the parent compound has been observed (ECETOC, 2005).

The metabolic pathway is shown in figure 1. The main metabolite is 2-methoxyethoxyacetic acid. The reproductive toxicity of diglyme is attributed to the minor metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol. The metabolite 2-methoxyacetic acid has shown evidence of accumulation in animals and humans. In humans its half-life was calculated as 77.1h (ECETOC, 1995, WHO, 2002).

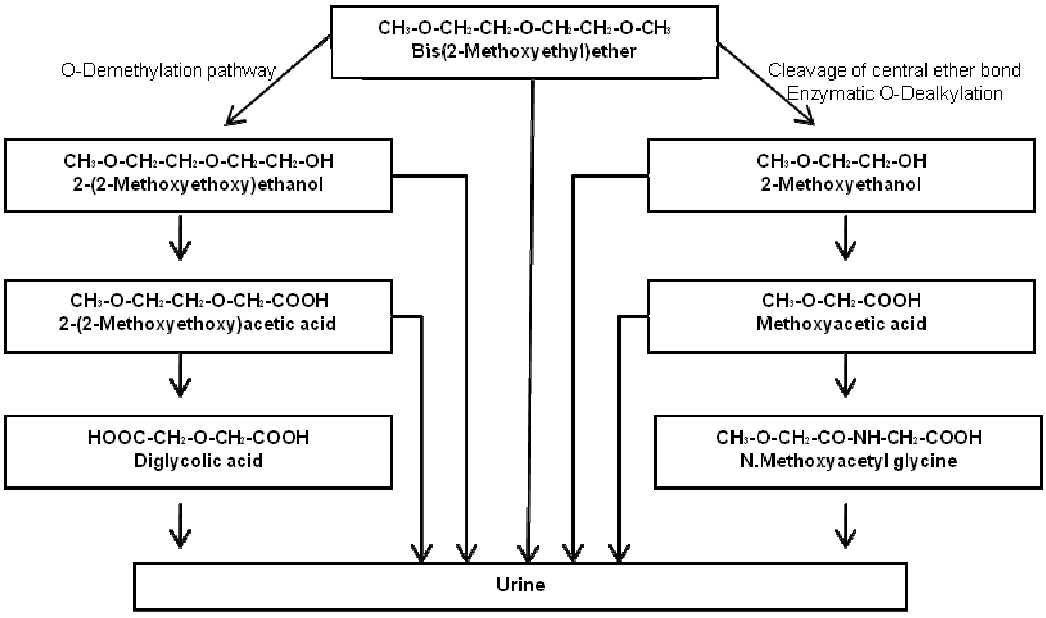


**Figure 1: Metabolism and disposition of diglyme (WHO, 2002; Sullivan, 2001).**

Digyme is a developmental toxicant in rats and mice but at higher doses, compared to other glycol ethers. This may be explained by the low levels of the metabolites 2-methoxyethanol (EGME) and methoxyacetic acid (MAA) formed (ECETOC, 2005).

# 9 TOXICITY FOR REPRODUCTION

## 9.1 Effects on fertility

The reproductive organs of male animals are a specific target for diglyme. Several well conducted studies are available and summarized in Table 19.

From these studies the NOAEL for effects on the testis/spermatocytes is 30ppm (167mg/$m^3$).

## 9.2 Developmental toxicity

Diglyme is a developmental toxicant by the inhalatory and the oral route in rat, mice and rabbits. An overview of relevant studies is given in Table 20 (key study) and Table 21.

Oral exposure of New Zealand White rabbits to diglyme at 25mg/kg bw/day produced no adverse maternal or developmental effects. Doses of 50 and 100mg/kg bw/day were associated with adverse developmental effects but did not produce distinctive evidence of maternal toxicity. At 175mg/kg bw/day developmental effects were accompanied by increased maternal toxicity. The principal manifestations of developmental toxicity were increased resorptions and higher incidence of major malformations among surviving foetuses with a $NOAEL_{fetal}$ of 25mg/kg bw/day (NTP, 1987). In 1992 Schwetz et al. published the NTP data with a diverging interpretation of the results showing a dose related developmental toxicity with a $NOAEL_{maternal}$ of 25mg/kg bw/day and a $NOAEL_{fetal}$ of 50mg/kg bw/day.

# 10 ENVIRONMENT

Diglyme is not classified as hazardous to the environment. The EU-Working Group has decided that there are insufficient data in order to classify (SUMMARY RECORD Commission Working Group on the Classification and Labelling of Dangerous Substances, 1999, ECBI/60/99 Rev. 4).

The available registration data support the non-classification for environmental effects.

**Table 7: Fertility, study overview.**

| Species | Route of exposure | Dose/ Concentration | Observations, effects | NOAEL | Reference |
|---|---|---|---|---|---|
| rat (Crl:CD) male<br>20 animals/group | Inhalation<br>6h/day<br>5days/week<br>for 2 weeks<br>84 days post exposure | 0, 110, 370, 1100ppm | **370ppm (2065mg/m$^3$ ) and 1100ppm**: absolute weight of testis, epididymides. Seminal vesicles and prostate ↓<br>**1100ppm (6138mg/m$^3$):** relative weight of testes ↓, testicular atrophy (all spermatogenic stages affected)<br><br>Effects were reversible within 84 days (but not at 1100ppm). | | DuPont (1988b), Valentine et al., (1999) |
| rat (Crl:CD) male<br>20 animals/group | Inhalation<br>6h/day<br>5days/week<br>for 2 weeks<br>14 days post exposure | 0, 3, 10, 30, 100ppm | Some effects (degenerative germ cells in epididymal tubules, spermatic granuloma in the epididymis, prostatitis) occurred at concentrations below 100ppm, most lesions were minimal to mild. It is not clear whether the different lesions observed occurred in the same or different animals.<br>**100ppm (558mg/m$^3$):** mean body weight ↓, mild testicular atrophy | 30ppm (167mg/m$^3$) | DuPont (1989) |
| rat (CD)<br>male<br>10 animals/group | Inhalation<br>7h/day<br>5days | 0, 250, 1000ppm | Dominant lethal test (males were mated at weekly intervals for 10 weeks with untreated females, females killed 17days after mating)<br>**1000ppm (5580mg/m$^3$)**: reduced body weight in male rats; pregnancy frequency in mated female rats was only | | McGregor et al. (1981, 1983) |

| | | | | | |
|---|---|---|---|---|---|
| | | | about 10% in week 5 to 7 after exposure, preimplantation losses<br>Recovery in exposed males was completed in week 10. | | |
| mice (B6C3F1) | Inhalation<br>7h/day<br>4 days | 0, 250, 1000ppm | Sperm isolation on day 35 after exposure<br>Mice of both exposure groups showed a reduction in body weight gain. 4 mice of 1000ppm exposure group died on exposure day 4.<br>**1000ppm:** morphologically altered sperm (32%; control 5%) (all categories of abnormalities involved but most frequent were amorphous heads) | | McGregor et al. (1981, 1983) |
| rats (Sprague-Dawley)<br>male<br>5 animals per group | Oral<br>20 days | 684mg/kg bw<br>8week recovery | Primary and secondary spermatocyte degeneration, spermatidic giant cells, reduced testis to body weight ratio from day 12 till end of study, testicular LDH-X activity by day 18 ↓ | | Cheever at al. (1985, 1989) |

↓ decreased compared with controls
↑ increased compared with controls

**Table 8: Developmental toxicity, key study, overview (according to WHO, 2002).**

| Species | Route of exposure | Dose/ Concentration | Observations, effects | Maternal NOAEL | Fetal NOAEL/ LOAEL | Reference |
|---|---|---|---|---|---|---|
| Rabbits (New Zealand)<br>Female<br>15-25 animals/group | Gavage in distilled water<br>Days 6-19 | 0, 25, 50, 100, 175mg/kg bw | **50 mg/kg body weight**: dams: weight gain ↓ (due to decrease in gravid uterine weight), adversely affected implants per litter ↑ (21.4%, controls 7.9%)<br><br>**100 mg/kg body weight**: gravid uterine weight ↓, prenatal mortality (mainly from resorptions) ↑, malformations ↑ (mainly abnormal development of the kidneys and axial skeleton and clubbing of the limbs)<br><br>**175 mg/kg body weight:** dams: faecal output ↓, mortality ↑ (15%, controls 4%) Evidence of maternal toxicity was observed only at 175mg/kg/day.<br><br>*New evaluation of NTP (1987) performed by Schwetz et al.(1992)* | NOAEL 100mg/kg bw<br><br>NOAEL 25mg/kg bw | NOAEL 25mg/kg bw<br><br>NOAEL 50mg(kg bw | NTP (1987) cited in WHO, 2002<br><br>Schwetz et al. (1992) |

↓ decreased compared with controls
↑ increased compared with controls

**Table 9: Developmental toxicity, additional studies, overview (according to WHO, 2002).**

| Species | Route of exposure | Dose/ Concentration | Observations, effects | Maternal NOAEL | Fetal NOAEL/LOAEL | Reference |
|---|---|---|---|---|---|---|
| Rats (CD), female<br>25-26 animals/group | Inhalation<br>6h/day<br>days 7-16 | 0,25, 100, 400ppm<br>(0, 140, 558, 2232mg/m³) | **25 ppm (140 mg/m3)**: fetal weights ↓, variations (delayed ossification, rudimentary ribs) (mean percentage of fetuses per litter with variations): 44.5% versus controls 32.1%<br><br>**100 ppm (558 mg/m3)**: dams: relative liver weight ↑, fetus: structural malformations, mainly skeletal (abnormally formed tails, distended lateral brain ventricles, axial skeletal malformations, appendicular malformations [bent limbs], 6.2% compared with 1.7% in controls); fetal weight ↓; variations (mean percentage of fetuses per litter with variations): 74.5% versus controls 32.1%<br><br>**400 ppm (2232 mg/m3)**: dams: food consumption ↓, body weight gain ↓; resorptions 100% | NOAEL 25ppm (140mg/m³) | LOAEL 25ppm (140mg/m³) | DuPont (1988a) cited in WHO, 2002<br>Driscoll et al. (1998) |
| mice CD-1 | gavage in distilled | 0, 62.5, 125, 250, 500 mg/kg | **125 mg/kg body weight**: fetal weights ↓ | NOAEL | NOAEL 62.5 mg/kg | NTP (1985), Price et al. |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20–24 animals/group | water, days 6–15 | bw | **250 mg/kg body weight**: dams: weight gain ↓ (due to decrease in gravid uterine weight); late fetal deaths ↑, malformations ↑ (mainly neural tube, limbs and digits, craniofacial structures, abdominal wall, cardiovascular system, urogenital organs, axial and appendicular skeleton)<br><br>**500 mg/kg body weight**: dams: weight gain (due to decrease in gravid uterine weight) ↓; resorptions ↑ | 500 mg/kg bw | bw | (1987) |
| mice CD-1 not given | gavage in distilled water, single application on day 11 | 0, 537 mg/kg bw | only examination for gross external malformations and fetal body weight<br>**537 mg/kg body weight**: malformations ↑ (paws, digits) | | | Hardin et al. (1986, 1987) |
| mice CD-1 49 animals/group | gavage in distilled water, days 6–13 | 0, 3000 mg/kg bw | reproductive screening according to Chernoff and Kavlock, no systematic examination for malformations<br><br>**3000 mg/kg body weight**: dams: mortality ↑ (20/49); no viable litters (0/27) | | | Schuler et al. (1984), Plasterer et al. (1985), Hardin et al. (1987) |

↓ decreased compared with controls
↑ increased compared with controls