2-(2-Methoxyethoxy)ethanol (DEGME)

Evaluation of the effects on reproduction, recommendation for classification

To: the State Secretary of Social Affairs and Employment
No. 2017/21, The Hague, November 21, 2017

Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad de effecten van de stof dietyleenglycol (mono)methylether (DEGME) op de voortplanting beoordeeld.
Dit advies is opgesteld door de commissie Classificatie reproductietoxische stoffen – hierna aangeduid als de commissie – een subcommissie van de vaste commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS).
De Gezondheidsraad heeft een vaste rol bij de bescherming van werknemers tegen mogelijke schadelijke effecten van stoffen waar zij tijdens hun werk mee in aanraking kunnen komen. Meer informatie over die rol staat op www.gezondheidsraad.nl.

Gebruik van DEGME

DEGME wordt voornamelijk gebruikt als hulpmiddel in de industrie en als toevoeging aan brandstof voor vliegtuigen. Het gebruik als oplosmiddel voor coatings is de afgelopen jaren afgenomen en komt alleen nog voor in de gespecialiseerde industriële markt. In beperkte mate DEGME wordt ook professioneel gebruikt in drukinkt en textielverf.

Classificeren naar bewijskracht voor schadelijk effect

Bij de beoordeling van effecten op de voortplanting, kijkt de commissie zowel naar de effecten op de fertiliteit (vruchtbaarheid) van mannen en vrouwen als naar de effecten op de ontwikkeling van het nageslacht. Daarnaast worden de effecten op de lactatie (hoeveelheid en kwaliteit van moedermelk) beoordeeld en de effecten via de moedermelk op de zuigeling.

De commissie beoordeelt of er aanwijzingen zijn dat de stof een schadelijk effect kan hebben. Als dergelijke aanwijzingen bestaan stelt ze voor om de stof in te delen in een bepaalde categorie, die aangeeft hoe sterk de bewijskracht is voor het schadelijke effect van de stof. Op basis van dat voorstel kan de minister van SZW de stof al dan niet classificeren als reproductietoxische stof. De classificatie is gebaseerd op EU-verordening (EG) 1272/2008.

Advies aan de staatssecretaris

Op grond van de beschikbare wetenschappelijke onderzoeken stelt de commissie voor om DEGME alleen te classificeren voor effect op de ontwikkeling. Over de effecten op de vruchtbaarheid en op of via lactatie zijn onvoldoende gegevens beschikbaar van onderzoeken bij mensen of bij dieren.

Classificatievoorstel commissie voor dietyleenglycol (mono)methylether (DEGME):

- voor effecten op de fertiliteit: niet classificeren wegens onvoldoende geschikte gegevens
- voor effecten op de ontwikkeling: classificeren in categorie 1B (stoffen waarvan verondersteld wordt dat zij toxisch zijn voor

de menselijke voortplanting) en etiketteren met H360D (kan het ongeboren kind schaden)

- voor effecten op of via lactatie: niet etiketteren wegens onvoldoende geschikte gegevens.

executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council evaluated the effects on reproduction of the substance 2-(2-methoxyethoxy)ethanol (DEGME).
This advisory report has been drafted by the Health Council's Subcommittee on the Classification of reproduction toxic substances of the Dutch Expert Committee on Occupational Safety (DECOS), hereafter referred to as the Committee. The Health Council has a permanent task in assessing the hazard of substances to which man can be occupationally exposed. More information on this task can be found at www.gezondheidsraad.nl.

Uses of DEGME

DEGME is primarily used as an intermediate or industrial processing aid and an additive in aviation fuels. Previous use in coatings has declined substantially, remaining only in specialist industrial markets and in professional uses such as specialist printing inks and textile dyes. These uses concern amounts small in volume.

Classification based on level of evidence for hazardous effect

When evaluating the effects on reproduction, the Committee takes into account effects on male and female fertility and on the development of the progeny. Moreover, the Committee considers the effects of a substance on lactation and on the progeny via lactation.

If there are data indicating hazardous properties, the Committee recommends classification in a category based on the strength of the evidence. Based on that proposal, the minister of Social Affairs and Employment decides whether to classify the substance as toxic to reproduction. The classification is performed according to EU-regulation (EC) 1272/2008.

Recommendation to the State Secretary

Based on the available scientific data, the Committee proposes to classify DEGME for effects on development. There are insufficient data available with regard to the effects on fertility and effect on or via lactation in humans or animals.

The Committee's proposal for classification of DEGME:

- for effects on fertility: not to classify due to a lack of appropriate data
- for effects on development: to classify in category 1B (suspected human reproductive toxicant) and label with H360D (may damage the unborn child) according to Regulation (EC) 1272/2008.
- for effects on or via lactation: not to label due to a lack of appropriate data.

01 scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on April 1, 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. This classification is performed by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety (DECOS). The classification is performed according to European Union Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. The CLP regulation is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The Subcommittee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of substances classified as reproductive toxicant (category 1A and 1B and 2) or with effects on or via lactation.

The ministry of Social Affairs and Employment asked the Health Council to update the evaluation and classification on reproduction toxicity for a series of substances. In this report, submitted November 21, 2017, such an update was performed for 2-(2-methoxyethoxy)ethanol (DEGME). An evaluation of this substance was published previously in 2003, in a report on diethyleneglycol (mono)alkylethers.[1]

1.2 Committee and procedure

This document contains the recommendations for classification of DEGME by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee. The members of the Committee are listed on the website of the Health Council. The classification is based on the evaluation of published human and animal studies, including those available in the REACH registration dossier, concerning adverse effects with respect to fertility and development as well as effects on or via lactation.

Classification for reproduction (fertility (F) and development (D):	
Category 1	Known or presumed human reproductive toxicant (H360(F/D))
Category 1A	Known human reproductive toxicant
Category 1B	Presumed human reproductive toxicant
Category 2	Suspected human reproductive toxicant (H361(f/d)
No classification for effects on fertility or development	
Classification for lactation:	
	Effects on or via lactation (H362)
	No classification for lactation
Hazard statement codes:	
H360F	May damage fertility
H360D	May damage the unborn child
H361f	Suspected of damaging fertility
H361d	Suspected of damaging the unborn child
H360FD	May damage fertility. May damage the unborn child
H361fd	Suspected of damaging fertility. Suspected of damaging the unborn child
H360Fd	May damage fertility. Suspected of damaging the unborn child
H360Df	May damage the unborn child. Suspected of damaging fertility
H362	May cause harm to breastfed babies

The classification and labelling of substances is performed according to the criteria of the European Union (Regulation (EC) 1272/2008). The classification of substances is the result on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations.

Additional considerations to Regulation (EC) 1272/2008

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see regulation (EC) 1272/2008, 3.7.2.2.1.).
- Adverse effects in a reproductive study, reported without information on the parental or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in general toxicity studies.
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- The Committee does not only use guideline studies (studies performed according to OECD[a] standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

[a] Organization for Economic Cooperation and Development

In 2016, the President of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the report. These comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Labelling for lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The criteria define that substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and developmental effects, which is based on hazard identification only (largely independent of dosage), the classification for effects during lactation is based on a risk characterization and therefore, it also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be classified for effects during lactation when it is likely that the substance would be present in breast milk at potentially toxic levels. The Committee considers a concentration of a substance as potentially toxic to the breastfed child when this concentration leads to exceeding the exposure limit for the general population, e.g. the acceptable daily intake (ADI).

1.4 Data

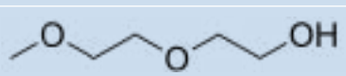
Literature searches were conducted in the on-line databases XTOXLINE, MEDLINE and CAPLUS, up to May 2017. The ECHA database on registered substances was consulted as well. Publications cited in the selected articles, but not selected during the primary search, were

reviewed if considered appropriate. In addition, handbooks and most recent reviews were consulted.
The Committee describes both human and animal studies in the text. Of each study, the quality of the study and the level of documentation are considered in a qualitative manner. The Committee outlines its considerations in the text, where appropriate.

02 identity of the substance

The identity and physicochemical properties of 2-(2-methoxyethoxy) ethanol (DEGME) are given below.[1-3]

2.1 Name and other identifiers of the substance

EC/EINECS number	:	203-906-6
EC name	:	2-(2-methoxyethoxy)ethanol
CAS number	:	111-77-3
CAS name	:	2-(2-methoxyethoxy)ethanol
IUPAC name	:	2-(2-methoxyethoxy)ethanol
Synonyms	:	DEGME; methyldiglycol; diethyleneglycol (mono)methyl ether; diglycol monomethyl ether; 3,6-Dioxa-1-heptanol
CLP Annex VI index number	:	603-107-00-6
Molecular formula	:	$C_5H_{12}O_3$
Molecular weight	:	120.2
Structure	:	

2.2 Composition of the substance

Not applicable.

2.3 Physico-chemical properties

State of the substance at normal temperature and pressure	:	Colourless liquid
Melting/freezing point	:	-65°C
Boiling point	:	190-196°C
Density	:	1.02 kg/dm^3
Vapour pressure	:	≤ 0.24 hPa at 25°C
Surface tension	:	34.8 mN/m
Water solubility (at room temperature)	:	miscible
Log P (octanol-water)	:	-0.682 (unclear whether experimental or estimated)
Flash point	:	91°C
Autoflammability	:	215°C (self-ignition temperature)
Explosive limits	:	-
Oxidizing properties	:	-
Stability in organic solvents and identity of relevant degradation products	:	-
Dissociation constant	:	pKa is ca. 15
Conversion factor	:	1 ppm = 5.0 mg/m^3 at 760 mm Hg and 20°C 1 mg/m^3 = 0.2 ppm

2.4 International classifications

The harmonized EU classification of DEGME is Repr. 2, with hazard statement H361d (data derived from European Chemicals Agency: http://echa.europa.eu/). DEGME is restricted in marketing and use (REACH Annex XVII; entry 54).

03 manufacture and uses

3.1 Manufacture

Not relevant for classification.

3.2 Identified uses

DEGME is primarily used as an intermediate or industrial processing aid and an additive in aviation fuels. Previous use in coatings has declined substantially, remaining only in specialist industrial markets and in professional uses such as specialist printing inks and textile dyes. These uses are small in volume. The use of hydrolic fluid has also been reported. As DEGME is relatively non-volatile, human exposure most likely occurs via the dermal route.

04 toxicokinetics (absorption, metabolism, distribution and elimination)

In this section, the Committee provides a short summary based on the European Risk Assessment Report.[3] Additional references are specified separately.

A limited amount of data is available on the toxicokinetics of DEGME. Dermal absorption was only investigated in in vitro assays. With human skin, an absorption rate of 0.21 ± 0.16 mg/cm^2/h was found for 98% pure DEGME.[4] Using rat skin, an absorption rate of 0.05 ± 0.02 mg/cm^2/h was reported.[5] No data on absorption after exposure by inhalation are available. In an assessment of the urinary metabolic profile of DEGME, 95% of the orally administered doses (500, 1,000 and 2,000 mg/kg bw) was recovered in 48 h, the majority within the first 24 h.[8]

Data on the group of glycol ethers indicate that two main pathways of metabolism exist, one involving alcohol dehydrogenase and one involving microsomal P450 mixed function oxidation.[6] The first pathway results in alkoxy acetic acids, whereas the second results in the formation of carbon dioxide via ethylene glycol or propylene glycol. 2-Methoxyacetic acid belongs to the group of alkoxyacetic acids, which are reported to be eliminated slowly[6], and possibly slower in humans than in rats[7].

An excretion and metabolism study has been conducted with DEGME.[8] Male Sprague-Dawley rats were administered a single dose of 500, 1,000, or 2,000 mg/kg bw by gavage. Urine was sampled during the periods 0-24 h and 24-48 h. Analysis was done using liquid chromatography-tandem mass spectrometry. The following metabolites were detected:

Table 4.1. Results of the DEGME metabolism study in rats

Dose	500 mg/kg		1,000 mg/kg		2,000 mg/kg	
	% (sd)	mg/kg (sd)	% (sd)	mg/kg (sd)	% (sd)	mg/kg (sd)
Methoxyethoxyacetic acid (MEAA)	94.5 (7.5)	472.5 (37.5)	90.9 (8.5)	909.0 (7.7)	87.2 (4.5)	1,744.0 (90.0)
Methoxyacetic acid (MAA)	1.4 (0.1)	7.0 (0.5)	1.1 (0.1)	11.0 (0.1)	0.8 (0.1)	16.0 (2.0)
Diethylene glycol (DEG)	2.9 (0.4)	14.5 (2.0)	2.3 (0.8)	23.0 (0.7)	2.2 (0.4)	44.0 (8.0)
DEGME-Glucoronide	1.0 (0.1)	5.0 (0.5)	0.8 (0.1)	8.0 (0.1)	0.7 (0.1)	14.0 (2.0)
DEGME	3.4 (0.4)	17.0 (2.0)	3.6 (0.7)	36.0 (0.1)	4.9 (0.7)	98.0 (14.0)
Total	103.3 (7.1)	516.5 (35.5)	98.7 (7.3)	987.0 (6.6)	95.9 (3.8)	1,918.0 (76.0)

Conclusion

DEGME appears to be readily absorbed through the skin, with an estimated absorption rate of 0.05-0.21 mg/cm^2/h. A metabolism study in rats showed that orally administered DEGME is primarily metabolized to and excreted via the urine as MEAA, and to a limited extent as MAA and DEG.

05 toxicity for reproduction

5.1 Adverse effects on sexual function and fertility

Table 5.1. Summary table of animal studies on adverse effects on sexual function and fertility

reference	species	experimental period/design	dose/route	general toxicity	effects on reproductive organs/ effects on reproduction
Miller et al., 1985[9]	Rat, Fischer (n=10/group; M+F; 6-8 weeks old)	Exposure for 6 hours per day, 5 days/week, for 13 weeks. Gross pathological and histopathological examination (including testis, epididymis, seminal vesicle, prostrate, coagulating gland, ovary, oviduct, uterus, cervix and vagina).	0, 150, 500 or 1,080 mg/m^3/ day (0, 30, 100 or 216 ppm); inhalation.	Not observed.	No effects on reproductive organs (gross pathology and histopathology).
Cheever et al., 1988[10]	Rat, Sprague-Dawley (n=50/group; M; age not described)	Daily exposure for up to 20 days. At 2-day intervals on days 3 through 21 5 rats were sacrificed. Histopathological examination of the testes.	613 mg/kg bw/day; gavage.	Not described.	No gross or microscopic abnormalities of the testes were detected.
Kawamoto et al., 1990[11]	Rat, Wistar (n=4-8/group; M; age not described)	Daily exposure for 20 days. Thymus and testis were weighed.	0, 500, 1,000 and 2,000 mg/kg bw/day; gavage.	2,000 mg/kg bw/day: reduced body weight ($p<0.05$); 1,000 and 2,000 mg/kg bw/day: reduced thymus weight ($p<0.01$ and $p<0.05$, respectively).	2,000 mg/kg bw/day: reduced relative testis weight ($p<0.05$).
Kawamoto et al., 1990[11]	Rat, Wistar (n=4-8/group; M; age not described)	Daily exposure for 1, 2, 5 or 20 days. Weight gain and weights of liver, kidney, spleen, thymus, heart , lung and testis recorded.	0 and 2,000 mg/kg bw/day; gavage.	2,000 mg/kg bw/day: reduced body weight ($p<0.05$); reduced relative thymus weight (at day 5 and 20, $p<0.05$ and $p<0.01$, respectively); reduced relative liver weight (at day 5 and 20, $p<0.05$).	Decrease in relative weight of testis after 5 and 20 days of dosing ($p<0.05$).
ECHA, 2016[12]	Rat, CR, COBS, CD, BR albino (n=10/group; M; 236 g)	Exposure for 6 weeks (5 days/week). Signs of systemic toxicity, appearance and behaviour were monitored. After sacrifice, haematology, clinical chemistry, gross pathology and histopathology were performed.	0, 900, 1,800 or 3,600 mg/kg bw/day; gavage.	At 3,600 mg/kg bw/day: Reduced body weight, increased kidney and heart weight (relative) and reduced spleen, liver and brain weight (absolute). At 1,800 mg/kg bw/day: increased heart weight (relative) and reduced liver weight (absolute).	At 3,600 mg/kg bw/day: reduced testis weight (relative); at 1,800 mg/kg bw/day: increased testis weight (relative). Testicular atrophy was seen in 6/10 high dose animals half of which also had accompanying degenerated spermatozoa in the epididymides and hypospermia.
Hobson et al., 1986[13]	Guinea pig, Hartley (n=6/group; M; 6-8 weeks)	Exposure for 90 days (5 days/week, 6 hours/day).	0, 40, 200, 1,000 mg/kg bw/day; dermal.	No effect on body weights. Spleen weights decreased at 200 mg/kg bw/day and above ($p<0.05$). Mild fatty change in livers of all treated animals.	No effects seen in any of the examined organs or tissues, including testes. DEGME exposure did not result in testicular lesions, nor were the relative and absolute weights of the testes, seminal vesicles and the prostate affected.

5.1.1 Animal studies

No mating studies are available, but a number of non-guideline repeated dose toxicity studies are. These are summarized in Table 5.1 and described below.

Male and female Fischer rats (10/sex/group) were subchronically exposed by inhalation to DEGME vapour at concentrations of 0, 150, 500 or 1,080 mg/m^3 (0, 30, 100 or 216 ppm) 6 hours per day, 5 days/week, for 13 weeks.[9] Following exposure, all animals were weighed, sacrificed and subjected to a complete gross pathological and histopathological examination, including testis, epididymis, seminal vesicles, prostate, coagulating gland, ovary, oviduct, uterus, cervix and vagina. No exposure related mortality occurred during the course of the study. Furthermore, no apparent differences in body weights and in absolute and relative organ weights were observed between control and treated groups of animals. No effects of the treatment were seen in haematology, clinical chemistry analyses, urinalyses and the gross pathological and histopathological examinations.

In a study by Cheever et al., male Sprague-Dawley rats were treated daily with oral doses of 5.1 mmol/kg bw DEGME (613 mg/kg bw) for up to 20 days.[10] No early deaths or overt signs of toxicity were observed. Selected animals (5 rats per time point) were killed at 2-day intervals on days 3 through 21. Following gross and histopathological examination, it was concluded that no degenerative changes were observed in the testes of any of the treated animals when compared to controls.

In a time course study, male Wistar rats (4-8/group) were daily administered oral doses of 2,000 mg/kg bw/day DEGME by gavage for 1, 2, 5 and 20 days.[11] After sacrifice, the weights of the liver, kidney, spleen, thymus, heart, lung and testis were determined. After one day, the relative thymus weight was decreased whereas the relative kidney weight was increased after 2 days. Decreases in relative weights of the liver, spleen, thymus and testis were reported after 5 days of dosing. The decrease in thymus and testis weights was more pronounced after 20 days of treatment.

In an accompanying dose-response study with oral doses of 0, 500, 1,000 and 2,000 mg/kg bw/day (4-8/group) during 20 days, the weights of the testis and the thymus only were reported. DEGME was shown to reduce body weight gain at 2,000 mg/kg bw/day compared to the control group from day 10 onwards. No effect on testis weight was observed at doses of 500 and 1,000 mg/kg, but at 2,000 mg/kg the testis weight was reduced relative to the body weight. The relative thymus weight was decreased at 1,000 and 2,000 mg/kg bw.

In a repeated dose toxicity study, male rats (10/group) were administered 0, 900, 1,800 or 3,600 mg DEGME/kg bw/day by gavage for 6 weeks.[12a]

[a] This study was referenced by other sources as a repeated dose study by Krasavage and Vlaovic (1982). The Committee did not review the original study report, but used the information provided by ECHA.

Signs of systemic toxicity, appearance and behaviour were monitored. After sacrifice, haematology, clinical chemistry, gross pathology and histopathology were performed. At the highest dose, the relative testis weight was decreased and atrophy, accompanied by evidence of degenerated spermatozoa in the epididymus and hypospermia, was observed in 50% of the rats. At this dose, clear signs of systemic toxicity were reported.

In a subchronical study of Hobson et al. (1986), male Hartley guinea pigs (n=6) were dermally (occlusive) exposed to DEGME at doses of 0, 40, 200 and 1,000 mg/kg bw/day during 90 days (5 days/week, 6 hour/day).[13] Average body weight of exposed animals decreased in a dose-related manner, but it was not statistically significantly different from control animals. At the medium and high doses, the spleen weights (both relative and absolute) were decreased. At the highest dose level, an increase in serum lactate dehydrogenase (LDH) was observed. A mild change in liver fat was observed in all test treatment groups but not in the controls. DEGME exposure did not result in testicular lesions, nor were body weight and the relative and absolute weights of the testes, seminal vesicles and prostate affected.

5.1.2 Human data

No studies are available regarding the effects of DEGME on human fertility.

5.1.3 Other relevant data

A limited amount of DEGME is metabolised to MAA, which is classified for effects on fertility (Repr. Cat. 1B).

5.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Effects on reproductive organs were investigated in four studies with rats (three with males only), and in one study with male guinea pigs. No effects were found in the rat study by Miller et al., in which rats (both males and females) were exposed via inhalation up to 1,080 mg/m^3 for 13 weeks.[9] In another study, oral exposure to 613 mg/kg bw/day up to 20 days did not lead to effects on the rat testes.[10] In a rat study reported by Kawamoto et al., decreases in relative weights of the testes were only seen at the highest dose level of 2,000 mg/kg bw/day for 20 days.[11] At this dose, relative body weight gain, relative thymus weight and relative liver weight were reduced. In a rat study summarised on the ECHA website, a reduced testis weight, testicular atrophy and sperm abnormalities were noted at 3,600 mg/kg bw/day.[12] At this dose, body weight was decreased, relative kidney and heart weights were increased, and absolute spleen, liver and brain weights were reduced. Guinea pigs were exposed dermally to up to 1,000 mg/kg bw/day, but this did not result in effects on the testes.[13]
No further studies are available on possible effects on fertility by DEGME. Taken together, it can be concluded that DEGME may have an effect on

testes weight and sperm in rats at oral doses 1,800 mg/kg/d and higher. In the other studies, the applied doses of 1,000 mg/kg bw/day and lower, did not affect the testes.

5.3 Comparison with the CLP criteria

No human data are available regarding the effects of DEGME exposure on fertility. In rats, male animals showed reduced testis weights (from 1,800 mg/kg bw and upwards), testicular atrophy and degenerated spermatozoa (at 3,600 mg/kg bw). These effects were accompanied by a reduction in bodyweight and organ weights. The Committee considers the upper dose not relevant, since the effects on testis weight can be a secondary effect due to general toxicity. No data are available on functional reproduction parameters.

In view of the absence of human data and relevant data on functional fertility in animals, the Committee concludes that a lack of appropriate data precludes the assessment of effect on fertility.

The Committee notes that a metabolism study with DEGME shows that limited amounts of 2-methoxyacetic acid is formed in rats.

2-Methoxyacetic acid has been reported to cause testicular damage in rats and mice (at single oral or i.p. doses of 118 mg/kg and higher), and to reduce fertility in mice (at doses of 140 mg/kg bw/day and higher)[14] and is therefore classified for effects on fertility (Repr. Cat. 1B).

5.4 Adverse effects on development

5.4.1 Animal studies

The developmental effects of DEGME on pregnant Sprague-Dawley rats (Crl:CD (SD) BR) were studied by Hardin et al.[15] Time-mated females were dosed by gavage with DEGME in distilled water on gestational days 7-16. Doses of 0, 1,000, 1,495, 2,235, 3,345, and 5,175 mg/kg bw/day were used in a preliminary dose-finding study with nine rats per group. Maternal weight was reduced in the highest dose group on days 16 and 21, and at 3,345 mg/kg bw/day on day 21. Extra gestational weight gain was reduced at the highest dose and two rats in this group died. Food consumption in the two highest dose groups was reduced during the first 5 days of exposure.

There were no live litters (0/5) in pregnant surviving animals at the highest dose, and only 3 live litters/9 pregnancies at 3,345 mg/kg bw/day. The percentage of live foetuses declined with increasing dose, and was reduced statistically significantly compared to the control group at 3,345 mg/kg bw/day. Similarly, foetal body weight consistently fell with increasing dose. An increased incidence of skeletal variations included rudimentary cervical or waivy/fused ribs at 2,235 mg/kg bw/day. Skeletal ossification was delayed at 1,495 mg/ kg bw/day and higher doses. The number of cardiovascular malformations was increased at 2,235 mg/kg bw/day.

Table 5.2. Summary table of animal studies on adverse effects on development

reference	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Hardin et al., 1986[15]	Rat, Sprague-Dawley (n=9/group; F; age not described)	Exposure on GD7-16, sacrifice on GD21. Body weights and food consumption were monitored. Foetuses weighed, gross pathology and histopathology.	0, 1,000, 1,495, 2,235, 3,345, 5,175 mg/kg bw/day; gavage (dose-finding).	5,175 mg/kg bw/day: maternal mortality (2/9) and reduction of extra gestational body weight gain ($p<0.05$).	3,345 and 5,175 mg/kg: reduction of percentage live birth per litter 10% and 0%, respectively (versus 91.2% in control group; $p<0.05$). 2,235 and 3,345 mg/kg: decreased foetal weight ($p<0.05$). Total number of skeletal variations in the vertebrae increased at 2,235 mg/kg bw/day ($p<0.05$ and $p<0.01$, respectively). Total visceral and cardiovascular malformations increased at 2,235 mg/kg bw/day ($p<0.05$).
Hardin et al., 1986[15]	Rat, Sprague-Dawley (n=12-13/group; F; age not described)	Exposure on GD7-16, sacrifice on GD21. Body weights and food consumption were monitored. Foetuses weighed, gross pathology and histopathology.	0, 720, 2,165 mg/kg bw/day; gavage.	2,165 mg/kg bw/day: decreased maternal weight ($p<0.05$).	At 2,165 mg/kg bw/day: decreased percentage live births per litter (60.5% versus 90.7% in control) with reduced foetal weight (both $p<0.05$); skeletal variations (ribs) and visceral (cardiovascular) malformations ($p<0.001$), several variations (including reduced ossification of various skeletal parts and urinary variations ($p<0.01$; $p<0.05$)). At 720 mg/kg bw/day: skeletal variations (ribs) and reduced ossification of the appendicular skeleton (both $p<0.05$); dilated renal pelvis ($p<0.05$).
Yamano et al., 1993[16]	Rat, Wistar (n=4-6/group; F; >3 months)	Exposure on GD7-17 and sacrificed on GD20. Position, number of live and dead foetuses (including resorptions) and number of corpora lutea were recorded.	0, 125, 250, 500, 1,000, 2,000, 3,000 and 4,000 mg/kg bw/day; gavage (dose-finding).	2,000 mg/kg bw/day and higher: reduced maternal weight gain 3,000 mg/kg bw/day and higher: reduced food consumption.	Dose-dependent decrease in number of live foetuses, no live foetuses at 3,00 and 4,000 mg/kg bw/day ($p<0.05$).
Yamano et al., 1993[16]	Rat, Wistar (n=14/group; F; >3 months)	Exposure on GD7-17 and sacrificed on GD20. Thymus and uterus (incl foetuses) of maternal animals were examined.	0, 200, 600, 1,800 mg/kg bw/day; gavage.	At 1,800 mg/kg bw/day: decrease of maternal body weight gain, food consumption, and thymus weight ($p<0.01$). At 200 and 600 mg/kg bw/day: no effects on dams reported.	At 1,800 mg/kg bw/day: Decreased number of live foetuses and increased incidence of dead or resorbed foetuses ($p<0.01$). Decrease in foetal body weight at 600 and 1,800 mg/kg ($p<0.05$ and $p<0.01$, respectively). At 1,800 mg/kg bw/day: external malformations ($p<0.01$), visceral malformations of the cardiovascular system ($p<0.01$), skeletal variations increased ($p<0.01$). At 600 mg/kg bw/day: variations in ossification of sternebrae and vertebrae ($p<0.01$).
	Rat, Wistar (n=8/group; F; >3 months)	Exposure on GD7-17 and sacrificed on 21 days postpartum. Pups were examined for growth and external differentation.	0, 200, 600, 1,800 mg/kg bw/day; gavage.		Prolonged gestational period and reduced number of live pups at 1800 mg/kg bw/day. Reduced viability of pups at 600 and 1,800 mg/kg bw/day.
Doe, 1984[17]	Rat, Alpk/AP (Wistar-derived) (n=15/group; F; 11-13 weeks)	Exposure on GD6-20. Pups examined and weighed on days 1 and 4 postpartum. No gross pathology or histopathology performed.	0, 250, 500, 1,000 µl/kg bw/day (0, 255, 510 and 1,020 mg/kg bw/day); subcutaneous.	Not described.	Non-statistically significant reduction in survival at PND5.

reference	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Schuler et al., 1984[18]	Mouse, CD-1 (n= 50/group; F; 6-8 weeks)	Exposure for 8 consecutive days starting GD7. Number of live-born pups, pup birth weight, growth and survival up to 2-3 days of age recorded.	4,000 mg/kg bw/day (established LD_{10}); gavage.	5/50 mice died; no further data on general toxicity.	Reduced percentage of viable litters (litters with one or more live-born pups/ number of pregnant survivors) to 16% (versus 97% in the control group). Reduced number of live pups per litter (3 in the DEGME group versus 10 in the control group; $p<0.05$) and pup survival over days 1 to 3 postpartum (31% in DEGME versus 100% survival in the control group; $p<0.05$).
Scortichini et al., 1986[19]	Rabbit, New Zealand White (n=25/group; F; age not specified)	Exposure on GD6-18. On GD 29, foetuses examined for external, visceral, and skeletal alterations.	0, 50, 250, 750 mg/kg bw/day; dermal (occlusive).	At 750 mg/kg bw/day 2/25 animals died and 1/25 at 50 mg/kg bw/day. Decreased weight gain at GD9-11 and haematological changes at 750 mg/kg bw/day ($p=0.05$).	At 750 mg/kg bw/day: developmental variations (mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs and delayed ossification of sternebrae; $p=0.05$). At 250 mg/kg bw/day and above: delayed ossification of the hyoid bone, delayed ossification of the cervical spur of the vertebrae ($p=0.05$).

Subsequently, pregnant rats were similarly dosed with 0, 720, or 2,165 mg/kg bw/day (12-13 rats per group). Maternal food consumption was reduced in the first 5 days of dosing and gross maternal weight was reduced on day 21 (93% of control) at 2,165 mg/kg bw/day. However, extra gestational weight gain was not influenced by DEGME treatment. Foetal body weights and the number of live implantations were reduced at 2,165 mg/kg bw/day and two of 23 litters were completely resorbed at that dose. There was no gross evidence of foetotoxicity at 720 mg/kg bw/day. Skeletal variations included rudimentary cervical ribs and bilateral wavy/ fused ribs, with the numbers of both of these being increased at 2,165 mg/kg bw/day. At 720 mg/kg bw/day, the incidence of combined rib variations was elevated. Retarded ossification was apparent in litters receiving the higher dose, and less markedly but still statistically significantly delayed ossification was also present in the 720 mg/kg bw/day dose group. Visceral malformations were predominantly seen in the cardiovascular system, and were statistically significantly increased at 2,165 mg/kg bw/day. One malformation of the heart was reported at 720 mg/kg bw/day.

In a dose-finding study by Yamano et al., Wistar rats were exposed by gavage to daily doses of 0, 125, 250, 500, 1,000, 2,000, 3,000 and 4,000 mg/kg bw/day DEGME.[16] The non-pregnant rats (5 rats/group) were treated for 11 consecutive days and pregnant rats (4-6/group) on days 7-17 of gestation. The non-pregnant rats showed a decrease in body weight gain and food consumption at doses above 3,000 mg/kg bw/day. Haematological measurements in the non-pregnant rats revealed decreased white and red blood cell counts, haemoglobin concentrations and haematocrit levels in a dose dependent way from 1,000 mg/kg bw/day

upward. There were no signs of hepatotoxicity, but at the highest dose, relative kidney weight and plasma blood urea nitrogen levels were slightly increased, indicating weak nephrotoxicity. Furthermore, dose-dependent decreases in weights of pituitary glands and thymus were observed. In pregnant rats, maternal body weight gain and food consumption were decreased above dose levels of 2,000 and 3,000 mg/kg bw, respectively. The number and body weight of live foetuses decreased in a dose-dependent way, with no live foetuses being seen at 3,000 and 4,000 mg/kg bw/day (total resorption of litters). Acidic urine was measurable at all doses.

Following this dose-finding study, female Wistar rats (14/group) were administered DEGME doses of 0, 200, 600 and 1,800 mg/kg bw/day by gavage from days 7 through 17 of gestation. On day 20 of gestation, dams were sacrificed. At 600 mg/kg, dams were not affected, but foetal body weights were decreased, and the incidence of foetuses with variations was increased. Among these variations, the incidence of thymic remnants in the neck was statistically significantly increased. At 1,800 mg/kg, maternal body weight gain, food consumption and maternal thymus weight were decreased, and visceral malformations of the cardiovascular system were observed in 28% of the foetuses. External malformations (mostly anasarca and anury) were observed in 14% of the foetuses at 1,800 mg/kg bw/day, but not at lower doses. Dilated renal pelvis was noted in 53% of the foetuses at the highest dose. The degree of ossification was considerably affected at 600 and 1800 mg/kg bw/day. In the same experiment, eight dams per group were administered doses of 0, 200, 600 and 1,800 mg DEGME/kg bw/day by gavage from days 7 through 17 of gestation. The duration of gestation was determined and litters were examined immediately after delivery (for litter size, stillborn and live born, sex and external anomalies). On day 4 after birth, culling was performed to leave eight pups per litter. Pups were nursed by their own mothers for 21 days and thereupon, pups and dams were sacrificed. In the highest dose group, the duration of gestation was prolonged by approximately 2 days and the number of pups was decreased. The viability of the neonates was markedly affected by the treatment with DEGME and the numbers of live pups on day 4 after birth divided by the numbers of live born pups were 92/100, 95/101, 58/93, and 2/37 for doses of 0, 200, 600 and 1,800 mg/kg, respectively. According to the authors, viability was only statistically significantly reduced at the highest dose. Body weight gain of pups during 21 days after birth was unaffected at 200 mg/kg bw/day, but slightly decreased at a dose of 600 mg/kg bw in each sex. No statistically significant effects of DEGME on the pups were found in the skeletal observations on day 21 postnatal either.

The effect of DEGME on foetal development when administered subcutaneously was investigated by Doe.[17] Pregnant Alpk/AP (Wistar-derived) rats were injected subcutaneously with 250, 500 or 1,000 µl/kg bw DEGME (255, 510 or 1,020 mg/kg bw/day) or a control solution, on days 6 to 20 of gestation. Rats were allowed to litter and the offspring was

weighed and the number of dead and live pups recorded on days 1 and 4 postpartum. No maternal toxicity was observed and little or no effect on the development of the pups at 250 µl/kg and 500 µl/kg. There was a slight, but not statistically significant decrease in survival of the offspring of the rats treated with 1,000 µl/kg. No gross pathology or histopathology on the offspring was performed.

Schuler et al. studied the effect of DEGME given by gavage during organogenesis in mice (CD-1 mice, n=50) in an in vivo screening test.[18] DEGME was given at 0 or 4,000 mg/kg bw in distilled water (determined to be the LD_{10}) once daily for 8 consecutive days starting on gestational day 7. Females were allowed to deliver litters, and the number of live-born pups, their birth weight, growth and survival up to 2-3 days of age were recorded. At this dose, 5/50 mice died. The percentage of viable litters was reduced to 16% (versus 97% in the control group). Furthermore, DEGME treatment was found to reduce the number of live pups per litter (3 versus 10 in the control group) and pup survival over days 1 to 3 postpartum (31% versus 100% survival in the control group). Pup birth weight was reduced to 88% of that of the controls and pup weight gain over days 1-3 was increased to 120% of that of the controls (not statistically significant).

Based on the results of a dose range finding study, female New Zealand White rabbits (25/group) were dermally (occlusive) exposed to undiluted DEGME at doses of 0, 50, 250, and 750 mg/kg bw/day from gestational days 6 to 18.[19] On gestational day 29, caesarian section was performed, followed by examination of the foetuses for external, visceral, and skeletal alterations. In the highest dose group, maternal toxicity was observed, characterized by decreased weight gain (during pregnancy day 9-11) and slight haematologic changes (i.e. decrease in red blood cells and packed cell volume values). Two of the 25 animals in the highest dose group died. At 250 and 50 mg/kg bw/day, no clinical signs of treatment-related maternal toxicity were observed. An increase in embryonic resorptions was noted at 750 mg/kg bw/day (not statistically significant). Foetal body weights were slightly lower in both the 250 and 750 mg/kg bw/day dose groups than in the controls. An increased prevalence of developmental variations was observed in foetuses in the two highest dose groups. These foetal alterations were mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs (at 750 mg/kg bw/day only) and delayed ossification of the skull and sternebral bones. The hyoid, delayed ossification of the skull and cervical spur of the vertebrae were also increased compared to the control group at 250 mg/kg bw/day. No adverse developmental effects were observed at the lowest dose (50 mg/kg bw/day).

5.4.2 Human data

One case report is available, in which a case of retrocaval ureter, with anomalies in both the cardiovascular and skeletal system is described.[20]

Since the mother was a worker in the textile industry, maternal exposure to DEGME was expected. As the report did not include blood concentration measurements or work place monitoring, however, no conclusions can be drawn about a possible correlation between the observed anomaly and exposure to DEGME.

5.4.3 Other relevant information

Scofield et al. performed an in vitro study to determine the effect of DEGME on the development of in vitro cultured forelimb cells isolated from chick embryo's.[21] After incubation for 5 days, only at the highest tested concentration (0.85 M) a stop in cell proliferation was detected, accompanied by total loss of proteoglycan. This effect was already seen after 24 hours, whereas the lower concentrations did not exhibit this effect. It is of note that DEGME's assumed metabolite methoxyacetic acid (MAA) was active two orders of magnitude lower. For MAA the effect was shown to be related to apoptosis, as seen by DNA fragmentation and upregulation of caspase activity.

In rats, a limited amount of DEGME is metabolised to MAA, which is classified for effects on development (Repr. Cat. 1B).

5.5 Short summary and overall relevance of the provided information on adverse effects on development

Only one report is available on possible human DEGME exposure to the mother of a child with congenital anomalies (retrocaval ureter), but no conclusions can be drawn.[20]

Developmental toxicity was investigated in three rat studies, one study with mice and one with rabbits. In two oral rat studies developmental effects were seen after exposure to DEGME.[15,16] Hardin et al. reported a reduction in live litters, malformations of the cardiovascular system (aortic arch and ventricular septum), variations of ribs (rudimentary and wavy/fused) and reduced foetal weight at relatively high doses (>2,000 mg/kg bw/day) that induced maternal weight loss, possibly due to loss of foetuses.[15] In the main study, at 720 mg/kg bw/day (and not in the dose finding study at 1,000 mg/kg bw/day), an increase of skeletal variations (total number of rudimentary and wavy/fused ribs) was observed in the absence of maternal toxicity. In the other rat study, by Yamano et al., no live litters were observed in a dose finding study at doses (3,000 and 4,000 mg/kg bw/day) that resulted in a reduced maternal body weight gain.[16] In the main study at 1,800 mg/kg bw/day, the incidence of resorptions was increased, malformations of the cardiovascular system (aortic arch; ventricular septum) and skeletal variations were found and foetal weight was reduced. At 600 mg/kg bw/day, a decrease in foetal weight and an increase in variations (both skeletal and, statistically not significant, visceral) were reported in the absence of maternal toxicity. A non-statistically significant reduction in survival of the offspring at PND5 was seen in rats after subcutaneous exposure to 1,000 µL/kg bw/day (1,020 mg/kg bw/day).[17] In the mouse study, mice were orally exposed to 4,000 mg/kg bw/day (corresponding to the LD_{10}).[18] Effects were seen in

the percentage of viable litters, the number of live pups per litter and pup survival over the first 3 days post partum. At this high dose, 10% of the exposed dams died during exposure. Rabbits were dermally exposed to DEGME up to 750 mg/kg bw/day.[19] At the highest dose, at which maternal toxicity was observed, a non-significant increase in embryonic resorptions and developmental variations was found. At 250 mg/kg bw/day, cranial variations were noted in the offspring in the absence of maternal toxicity.

5.6 Comparison with the CLP criteria

In several species, severe developmental effects were reported (i.e. reduced fetal viability in rats, mice and rabbits; increased visceral malformations in rats).

The severe effects observed in the mouse and the rabbit were observed at a dose level also inducing maternal lethality (approximately 10%). Therefore, these effects are likely to be secondary to the maternal toxicity (CLP criteria 3.7.2.4.3).

In two studies with rats, specific and severe developmental effects have been reported, that show a dose-response relationship.[15,16]

These responses were observed at relatively high doses (≥1,800 mg/kg bw/day), at which also effects on maternal body weight occurred. The Committee notes that it is not clear whether the reduction in maternal body weight is a direct effect or an indirect consequence of the observed reduction in foetal viability. At all doses, a slightly acidic urine was observed. The relevance of the developmental effects for classification should therefore be assessed (CLP criteria 3.7.2.5.7 and 3.7.2.5.9). The Committee is of the opinion that specific developmental effects, also at relatively high doses, should not be ignored based on limit dose considerations. It considers the occurrence of the cardiac malformations (malformations of the aortic arch; ventricular septal defects) in rats not causally related with the maternal toxicity reported. The Committee notes that cardiac malformations have also been observed in rats at doses below 1,000 mg/kg bw/day. One malformation of the aortic arch[15] and one ventricular septal defect[16] were observed at 720 and 600 mg/kg bw/day, respectively. Although not statistically significant at these dose levels, the Committee considers these effects suggestive of a dose-response relationship.

Also, an apparent but statistically non-significant reduction in postnatal viability was reported in rats at 600 mg/kg bw/day in the absence of maternal toxicity.[16]

Recently, 2-methoxyacetic acid has been confirmed as a metabolite of DEGME in rats.[8] 2-Methoxyacetic acid is classified in Category 1B for developmental toxicity and causes malformations of the heart (dilated ductus arteriosus and dilated aortic arch) at a single dose of 186 mg/kg bw/day and higher on GD12.[22] The Committee considers it plausible that the developmental effects in rats observed after exposure to DEGME are caused by its metabolite 2-methoxyacetic acid.

Finally, 2-methoxyacetic acid belongs to the group of alkoxyacetic acids, which are reported to be eliminated slowly6, and possibly slower in

humans than in rats.[7] This would imply that in humans, developmental effects might occur at lower external exposure levels than in rats.
Overall, the Committee concludes for DEGME that classification for developmental toxicity in Category 1B (presumed human reproductive toxicant) is warranted, based on cardiac malformations in the rat in the absence of maternal toxicity, and the observed formation of 2-methoxyacetic acid in potentially teratogenic amounts.

5.7 Lactation

5.7.1 Animal data

No studies were found regarding the effects of DEGME after lactational exposure in animals.

5.7.2 Human data

No studies are available regarding the effects of DEGME on human lactation.

5.8 Short summary and overall relevance of the provided information on effects on or via lactation

No data are available on effects of DEGME exposure on or via lactation.

5.9 Comparison with the CLP criteria

No data are available for comparison with the CLP criteria.

5.10 Conclusions on classification and labeling

Overall, the Committee proposes to classify 2-(2-methoxyethoxy)ethanol (DEGME) for effects on development. Based on the effects on development found in rats and rabbits, DEGME should be classified in category 1B (suspected human reproductive toxicant) and labelled with H360D (may damage the unborn child) according to Regulation (EC) 1272/2008.
In view of the absence of human data and relevant data on functional fertility in animals, the Committee proposes not to classify DEGME for effects on fertility.
No human or animal data were available for effects of DEGME through lactation. Therefore, no classification for effects on or via lactation is proposed.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of 2-(2-methoxyethoxy)ethanol (DEGME) for effects on fertility.

Proposed classification for developmental toxicity

Category 1B, H360D.

Proposed labelling for effect during lactation

Lack of appropriate data precludes the assessment of 2-(2-methoxyethoxy)ethanol (DEGME) for effects on or via lactation.

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