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Diethylene glycol dimethyl ether

MAK Value Documentation, supplement – Translation of the German version from 2021

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Keywords

diethylene glycol dimethyl ether; fertility; developmental toxicity; skin absorption; metabolism; toxicokinetics; maximum workplace concentration; MAK value

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value), the pregnancy risk group, sensitization, absorption through the skin and the germ cell mutagenicity of diethylene glycol dimethyl ether [111-96-6]. The critical effects of diethylene glycol dimethyl ether are its embryotoxic and fertility impairing effects, with the rat being the most sensitive species. The NOAEC for toxic effects on rat testes, derived from an inhalation study lasting only 2 weeks, is 30 ml/m^3. It is likely that the metabolites 2-methoxyethanol and 2-methoxyacetic acid are responsible for the reproductive toxicity of diethylene glycol dimethyl ether. The MAK value of 2-methoxyethanol was calculated to be 1 ml/m^3 on the basis of the BAT value of 2-methoxyacetic acid (15 mg 2-methoxyacetic acid/g creatinine). The MAK value of 2-methoxyacetic acid was established to be 1 ml/m^3 in analogy to 2-methoxyethanol. Based on these data, the MAK value for diethylene glycol dimethyl ether is set at 1 ml/m^3 (5.6 mg/m^3). This value also takes the increased respiratory volume at the workplace into account (see List of MAK and BAT values, Section I b and I c). As the critical effect is systemic and the critical metabolite 2-methoxyacetic acid has a long half-life, Peak Limitation Category II with an excursion factor of 8 is retained. In rats, there is an elevated incidence of skeletal variations without maternal toxicity after nose-only inhalation at 25 ml/m^3 and above. When the increased respiratory volume (1:2) is taken into account, the LOAEC of 25 ml/m^3 corresponds to 13 ml/m^3. The high (four-fold) foetal incidence of rudimentary lumbar ribs at this LOAEC indicates that the NAEC for developmental toxicity falls well below the required 10-fold margin to the MAK value. Therefore, the margin to the MAK value is not sufficient. The metabolite 2-methoxyethanol is teratogenic in rats, mice and rabbits and, at a MAK value of 1 ml/m^3, assigned to Pregnancy Risk Group B. After inhalation, the potency of diethylene glycol dimethyl ether for inducing skeletal variations is just as strong as that of 2-methoxyethanol. In addition, the half-life of the toxic metabolite 2-methoxyacetic acid in blood is longer in humans than in rats. Therefore, diethylene glycol dimethyl ether remains assigned to Pregnancy Risk Group B. A carcinogenicity study has not been performed with diethylene glycol dimethyl ether. Diethylene glycol dimethyl ether is not genotoxic. As it is possible to absorb toxic amounts through the skin, diethylene glycol dimethyl ether remains designated with “H”. Available data show no sensitization.

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MAK value (2020)	**1 ml/m³ (ppm) ≙ 5.6 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 8**
Absorption through the skin (1994)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1994)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value (2008) methoxyethanol	**15 mg methoxyacetic acid/g creatinine**
Chemical name (IUPAC name)	1-methoxy-2-(2-methoxyethoxy)ethane
CAS number	111-96-6
Structural formula	$H_3C–O–CH_2–CH_2–O–CH_2–CH_2–O–CH_3$
Molecular formula	$C_6H_{14}O_3$
Molar mass	134.17 g/mol
Melting point	−68 °C (ECHA 2019 a)
Boiling point at 1013 hPa	162 °C (ECHA 2019 a)
Density at 20 °C	0.94 g/cm³ (ECHA 2019 a)
Vapour pressure	0.6 hPa at 20 °C, 0.99 hPa at 25 °C (ECHA 2019 a)
log K_{OW}	−0.36 at 25 °C (ECHA 2019 a)
Solubility	940 g/l water at 20 °C
1 ml/m³ (ppm) ≙ 5.56 mg/m³	**1 mg/m³ ≙ 0.18 ml/m³ (ppm)**

Diethylene glycol dimethyl ether is subject to authorization because the substance induces reproductive toxicity (REACH, Annex IV; ECHA 2016).

Documentation for diethylene glycol dimethyl ether was published in 1994 (Greim 1998), followed by a supplement on peak limitation in 2001 (Greim 2001, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT values, Section IIb and IIc). A mean blood:air partition coefficient of 43 500 was calculated for diethylene glycol dimethyl ether by applying the formula of Buist et al. (2012). This supplement evaluates whether the MAK value and the pregnancy risk group for diethylene glycol dimethyl ether need to be amended because of the higher respiratory volume at the workplace.

This supplement includes only those toxicological end points for which new studies have become available since the documentation was published in 1994 (Greim 1998) in addition to the relevant end points for the re-evaluation of the

MAK value, the Pregnancy Risk Group, the sensitizing effects, absorption through the skin and for the evaluation of mutagenic effects on germ cells.

Mechanism of Action

Toxic effects on fertility

A number of studies have found that methoxyacetic acid and/or its metabolic precursor 2-methoxyethanol (ethylene glycol monomethyl ether) are responsible for the toxic effects on fertility induced by diethylene glycol dimethyl ether.

The product formed during the first step of the primary metabolic pathway is 2-(2-methoxyethoxy)ethanol (see Section "Metabolism" and Figure 1). This metabolite was not found to cause toxic effects on fertility in the most recent evaluation of the compiled study findings carried out by ECHA (2019 b). A second metabolic pathway forms 2-methoxyethanol and methoxyacetic acid via the cleavage of the central ether bond. These metabolites induce toxic effects and impair fertility, as was shown by comparative studies with oral administration of equimolar doses in rats (Cheever et al. 1986, 1989). Testicular atrophy was induced by diethylene glycol dimethyl ether (5 mmol/kg body weight and day, equivalent to 670 mg/kg body weight and day, 20 doses) and 2-methoxyethanol (5 mmol/kg body weight and day, equivalent to 380 mg/kg body weight and day, 2 doses), but not by 2-(2-methoxyethoxy)ethanol (5.1 mmol/kg body weight and day, equivalent to 612 mg/kg body weight and day, 20 doses) and (2-methoxyethoxy)acetic acid (5.1 mmol/kg body weight, equivalent to 684 mg/kg body weight and day, 20 doses). This confirms the findings of a comparative study that investigated the induction of testicular damage after 2-week inhalation exposure of rats that was not yet included in the documentation from 1994 (Greim 1998). The toxic effects on the testes caused by exposure to 2-methoxyethanol (direct metabolic precursor of methoxyacetic acid) at a concentration of 300 ml/m^3 were only slightly weaker than the effects induced by exposure to diethylene glycol dimethyl ether at 1100 ml/m^3 and much stronger than the toxicity induced by exposure to diethylene glycol dimethyl ether at 370 ml/m^3 (see Table 1) (Lee et al. 1989).

Tab. 1 Comparative study of testicular toxicity (testicular atrophy) after inhalation exposure of rats (Lee et al. 1989)

Substance	Concentration [ml/m^3]	Number of affected animals	% of affected seminiferous tubules	Assessment of testicular atrophy	Classification criterion: % of affected seminiferous tubules
DEGDME	0	2/5	< 10	+	< 10
	110	2/5	< 3	+	< 10
	370	5/5	10–20	++	10–40
	1100	5/5	80–90	++++	> 70
2-ME	300	5/5	25–80	+++	40–70

DEGDME: diethylene glycol dimethyl ether; 2-ME: 2-methoxyethanol

A 2-generation study carried out by the NTP in mice with the metabolite 2-methoxyacetic acid demonstrated the induction of marked adverse effects on fertility in male and in female animals (ECHA 2012; NTP 1986). In addition, a series of in vitro and in vivo studies on the mechanism of action of 2-methoxyacetic acid has shown that it influences the transcription mechanism of nuclear receptors, including the oestrogen and the androgen receptors, and modulates the expression of the oestrogen-responsive and androgen-responsive genes. Oestrogen and androgen receptors were more highly expressed in a spermatocyte apoptosis model in the rat testis. Anti-oestrogenic and progesterone modulatory responses have been reported in the mouse uterus. The toxic effects on the female and male reproductive systems and foetal development are attributed to the described disturbance of the hormonal balance (ECHA 2012).

Methoxyacetic acid binds to coenzyme A and enters intermediary metabolism as a false substrate. Like other inhibitors of the citric acid cycle, methoxyacetic acid reduces the lactate production in Sertoli cells. Pachytene spermatocytes are dependent on lactate, however. Other mechanisms have been suggested for the effects on the embryonal tissue such as

a possible lower availability of the smaller carbon compounds involved in purine or pyrimidine synthesis (ECETOC 1995). As the findings suggest that methoxyacetic acid impairs cell proliferation, the main target organs are tissues with a high rate of cell division such as the testes (sperm production), bone marrow (production of blood cells) and the developing foetus (Ferro Corp 2003).

In summary, the studies of testicular toxicity that have been carried out since the documentation was published in 1994 (Greim 1998) support the hypothesis that methoxyacetic acid is the metabolite of diethylene glycol dimethyl ether that causes the adverse effects on fertility.

Other mechanisms of action

In an in vitro study with human blood, the levels of haemolytic activity induced by diethylene glycol dimethyl ether and propylene glycol were low in comparison with the levels induced by dimethyl sulfoxide (very high), polyethylene glycol 200 (high), *N*-methyl-2-pyrrolidone and ethanol (moderate) (Mottu et al. 2001).

Toxicokinetics and Metabolism

Absorption, distribution, elimination

Diethylene glycol dimethyl ether is rapidly absorbed via the gastrointestinal tract, metabolized, and then excreted mainly with the urine. In mice, the substance was found to cross the placenta and reach the embryo (Greim 1998).

There are new data available for the absorption of the substance through the skin, which was determined in a study published in 1999 using Franz cells with human skin (donors: male and aged < 60 years). Diethylene glycol dimethyl ether (purity 99%) was tested in an amount of 0.2 ml either in undiluted form or as a 70% formulation in acetone. The substance was applied to a skin area of 3.14 cm^2 for an exposure period of 30, 60, 90, 120, 150, 180 or 240 minutes. The lag time of the undiluted substance was 36 minutes, the steady state flux 0.952 mg/cm^2 and hour and the permeability constant 1.016×10^{-3} cm/h. The corresponding values for diethylene glycol dimethyl ether in acetone were 49 minutes, 0.647 mg/cm^2 and hour and 1.141×10^{-3} cm/h (Larese Filon et al. 1999). Assuming exposure for 1 hour and a surface area of 2000 cm^2 (area of hands and forearms), the flux for undiluted diethylene glycol dimethyl ether would be equivalent to a maximum absorbed amount of about 2000 mg.

The toxic metabolite methoxyacetic acid was eliminated much more slowly in humans than by (pregnant) rats and monkeys. The half-lives in the blood of humans, rats and monkeys were 77, 12 and 19 hours, respectively (supplement "2-Methoxyethanol"; Hartwig 2009 b, available in German only).

Metabolism

In vivo

The metabolism of diethylene glycol dimethyl ether may follow two different reaction pathways. After a single dose of diethylene glycol dimethyl ether, the substance is metabolized predominantly by *O*-demethylation to yield 2-(2-methoxyethoxy)ethanol. Enzymes are induced after repeated exposure to diethylene glycol dimethyl ether, increasing NADPH-dependent cleavage of the central ether bond, which in turn leads to the formation of 2 molecules of 2-methoxyethanol. These are oxidized to methoxyacetic acid. After a single oral dose of diethylene glycol dimethyl ether was given to male rats, the primary metabolite was identified as (2-methoxyethoxy)acetic acid and accounted for 68% of the administered dose; the second metabolite, methoxyacetic acid, represented 6.2% of the dose. After repeated doses, the same fraction of (2-methoxyethoxy)acetic acid was identified and 10% was excreted as methoxyacetic acid (see Figure 1) (Cheever et al. 1988).

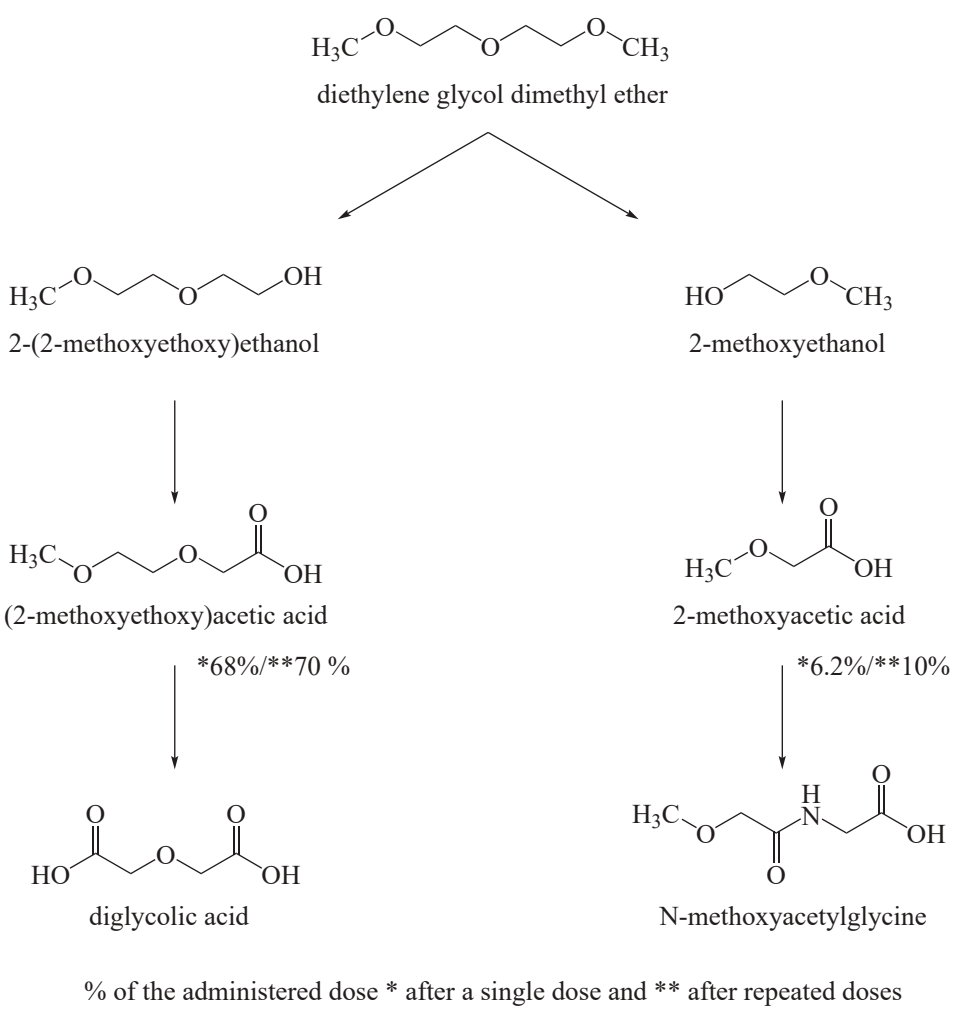

Fig. 1 Metabolism of diethylene glycol methyl ether in male rats after oral administration (according to Cheever et al. 1988)

Similar metabolic pathways were observed in studies with male rats and pregnant mice given oral doses of diethylene glycol dimethyl ether (Greim 1998).

In vitro

After the administration of 0.6% diethylene glycol dimethyl ether to rats with the drinking water for 4 days, the amount of 2-methoxyethanol formed in the liver microsomes after cleavage was 2.4 times as high as the levels determined after a single dose (Greim 1998).

New in vitro studies of enzyme induction have become available since the documentation was published in 1994 (Greim 1998). These are reviewed below.

A study investigated the induction of cytochrome P450 (CYP) activity, particularly CYP2E1 activity, in the liver microsomes of rats. The animals were given a diethylene glycol dimethyl ether dose of 2.5 mmol/kg body weight and day by intraperitoneal injection for 10 days and the microsomes from the liver were then isolated. CYP and cytochrome b5 levels were increased with statistical significance in comparison with the levels determined in the controls. Also aniline and *p*-nitrophenol hydroxylation, both reactions that are predominantly catalysed by CYP2E1, were increased with statistical significance in comparison with the levels of activity determined in the controls. A statistically

significant induction of NADPH-dependent CYP reductase or microsomal 2-methoxyethanol oxidation was not observed (Ferro Corp 1992).

Rat liver microsomes catalysed the NADPH-dependent cleavage of the central ether bond of diethylene glycol dimethyl ether yielding 2-methoxyethanol and 2-(2-methoxyethoxy)ethanol. Microsomes isolated from rats pretreated with phenobarbital or ethanol exhibited an increased capacity for cleavage. This ethanol-induced increase in 2-methoxyethanol formation was not observed if the CYP2E1 inhibitor isoniazid was added to the culture. Pretreatment of rats with diethylene glycol dimethyl ether significantly increased overall microsomal CYP levels and led to the increased conversion of diethylene glycol dimethyl ether to 2-methoxyethanol. Human hepatic microsomes likewise catalysed the NADPH-dependent cleavage of diethylene glycol dimethyl ether to 2-methoxyethanol. The formation of 2-methoxyethanol correlated with CYP2E1 activity (ECHA 2019 a).

After the incubation of isolated hepatocytes from male Sprague Dawley rats with diethylene glycol dimethyl ether in concentrations of 1, 10, 30 and 50 µM for up to 48 hours, the main metabolite was (2-methoxyethoxy)acetic acid and represented a fraction of about 67%. Other metabolites were 2-(2-methoxyethoxy)ethanol, methoxyacetic acid, 2-methoxyethanol and diglycolic acid. In this study, diethylene glycol dimethyl ether did not induce cytotoxic effects in rat hepatocytes (ECHA 2019 a).

Summary

The in vivo studies in rats and in vitro studies in rat hepatocytes and rat and human liver microsomes demonstrated that *O*-demethylation to form (2-methoxyethoxy)acetic acid is the preferred metabolic pathway. A repeated dose of diethylene glycol dimethyl ether or phenobarbital induced enzyme activity, thereby increasing NADPH-dependent cleavage of the central ether bond and the amount of excreted methoxyacetic acid (ECHA 2019 a; Greim 1998).

Effects in Humans

Reproductive and developmental toxicity

In two very extensive epidemiological studies that investigated exposure to different glycol ethers, the incidence of spontaneous abortions in exposed women was as high as 30% in comparison with 11% in women who were not exposed (Greim 1998).

A new epidemiological study became available in 1997 that investigated 44 children of workers employed at the same factory in a Mexican city. The workers were exposed to 2-methoxyethanol and monoethylene glycol without protective equipment. The cognitive skills of the children were found to be underdeveloped and musculoskeletal and sensory malformations were observed (ECETOC 2005).

As a result of the exposure to a mixture of substances and the absence of data for exposure levels, the studies cannot be used to evaluate the reproductive toxicity induced by diethylene glycol dimethyl ether.

Animal Experiments and in vitro Studies

Acute toxicity

Oral administration

The documentation from 1994 (Greim 1998) reported oral LD_{50} values of 4760 and 2978 mg/kg body weight for rats and female mice, respectively. The symptoms of toxicity were motor restlessness, breathing difficulties and reduced body weight gains.

A short report determined LD_{50} values higher than 1600 mg/kg body weight in groups of 3 rats given gavage doses of 50 to 1600 mg/kg body weight. Slight to moderate weakness was reported as the clinical symptom (no other details; Eastman Kodak Co 1991).

Another study in rats reported a lethal dose of about 7500 mg/kg body weight and day. One male CD rat was tested per dose. The animals that received doses of 1500, 2250, 3400 or 5000 mg/kg body weight survived the 14-day observation period. Lethargy, abdominal position and unkempt fur were the clinical symptoms observed at doses of 1500 mg/kg body weight and above, loss of body weight at 2250 mg/kg body weight and above and exhaustion at 5000 mg/kg body weight. The lethal doses were 7500 mg/kg body weight after 2 days, 11 000 mg/kg body weight after 1 day and 17 000 and 25 000 mg/kg body weight after 3 hours and 1 hour, respectively. Ataxia, loss of muscle tone, lethargy, exhaustion, breathing difficulties and abdominal position were observed at the lowest lethal dose and above. Pallor was noted at doses of 17 000 mg/kg body weight and above and loss of the righting reflex at 25 000 mg/kg body weight and above (Du Pont Chem 1992).

Allergenic effects

No studies with diethylene glycol dimethyl ether are available.

The ECHA dossier includes a local lymph node assay with diethylene glycol methyl ethyl ether that yielded negative results. The test was carried out according to OECD Test Guideline 429 with 25% and 50% formulations in acetone/olive oil (4:1) and in undiluted form. The stimulation indices determined for these concentrations were 0.73, 1.03 and 0.69, respectively (ECHA 2019 a).

Reproductive and developmental toxicity

Fertility

An inhalation study that was not included in the documentation from 1994 (Greim 1998) investigated the effects of diethylene glycol dimethyl ether on the male reproductive organs. The LOAEC (lowest observed adverse effect concentration) of this study was in the same range as those determined by previously described studies. After exposure of male rats to concentrations of 100 to 1000 ml/m^3 on 5 days a week for 2 weeks, a dose-dependent increase in testicular atrophy was determined at concentrations of 100 ml/m^3 and above, other toxic effects (no other details) at 600 ml/m^3 and above and reproductive toxicity at 1000 ml/m^3 (no other data; ECB 2000).

Developmental toxicity

No new studies of developmental toxicity have become available. The studies that were described in the documentation from 1994 (Greim 1998) are re-evaluated below taking current scientific knowledge into account. These are summarized in Table 2.

The ECHA dossier (2012) includes an overview of the studies; this shows that the same studies were published multiple times.

Inhalation

In female Crl:CD®BR rats that were exposed nose-only to diethylene glycol dimethyl ether concentrations of 0, 25, 100 or 400 ml/m^3 for 6 hours a day from days 7 to 16 of gestation, significant increases in liver weights were observed in the dams at 100 ml/m^3 and above and delayed body weight gains and reduced feed consumption at 400 ml/m^3. At concentrations of 25 ml/m^3 and above, the incidence of skeletal variations was increased in the foetuses, particularly delayed ossification and rudimentary ribs. At 400 ml/m^3, 100% of the foetuses were resorbed. The NOAEC (no observed adverse effect concentration) for maternal toxicity was 100 ml/m^3; a NOAEC for developmental toxicity could not be determined. In this study, one group of rats was exposed to a 2-methoxyethanol concentration of 25 ml/m^3 for

comparison. The structural variations observed were similar in incidence and severity to those induced by diethylene glycol dimethyl ether at a concentration of 25 ml/m^3. The two substances were therefore found to have a similar potency for inducing toxic effects on development (Driscoll et al. 1998; Du Pont de Nemours and Company 1988; Greim 1998). Noteworthy is the concentration-dependent increase in rudimentary lumbar ribs in the foetuses at the low concentration and above. At the lowest concentration tested of 25 ml/m^3, the incidence was already 4 times as high as the incidence in the controls.

The Commission used a benchmark calculation to determine a BMDL (benchmark dose lower confidence limit) of 15.1 ml/m^3 (log-logistic model, BMR 5% extra risk; 0.95% lower confidence limit, $p = 0.144$) for the number of affected foetuses with skeletal variations and a BMDL of 21.1 ml/m^3 (same model, $p = 0.326$) for the number with rudimentary lumbar ribs. None of the models was regarded as suitable for performing a benchmark calculation for rudimentary cervical ribs (for all models $p < 0.002$).

Oral administration

CD-1 mice were given diethylene glycol dimethyl ether in gavage doses of 0, 62.5, 125, 250 or 500 mg/kg body weight and day from days 6 to 15 of gestation. Maternal toxicity in the form of delayed body weight gains was observed at doses of 250 mg/kg body weight and day and above. The number of live foetuses per litter was reduced at the low dose of 62.5 mg/kg body weight and day and above. Foetal weights were reduced at doses of 125 mg/kg body weight and above and a significant increase in resorptions and malformations was observed at 250 mg/kg body weight and above (Greim 1998; Price et al. 1987). A NOAEL (no observed adverse effect level) of 125 mg/kg body weight and day was determined for maternal toxicity. The Commission regards the reduced number of implantation sites observed at 62.5 mg/kg body weight and day as coincidental because of the very large number of live foetuses per litter in the control group. For this reason, a NOAEL of 62.5 mg/kg body weight and day was determined for developmental toxicity.

Diethylene glycol dimethyl ether given to CD1 mice in a single gavage dose of 537 mg/kg body weight on day 11 of gestation did not induce maternal toxicity. The incidence of malformations of the hind paws was increased (Greim 1998; Hardin and Eisenmann 1987).

Diethylene glycol dimethyl ether given to CD1 mice in a gavage dose 3000 mg/kg body weight and day from days 6 to 13 of gestation led to complete foetal resorption at a concurrently high level of maternal mortality (Greim 1998; Hardin et al. 1987).

In New Zealand White rabbits given diethylene glycol dimethyl ether in gavage doses of 0, 25, 50, 100 or 175 mg/kg body weight and day from days 6 to 19 of gestation, maternal mortality was found to be increased at 175 mg/kg body weight. At doses of 50 mg/kg body weight and above, an increased percentage of adversely affected implantations (resorptions, foetal death, malformations) per litter were observed. Increased prenatal mortality, reduced foetal body weights and increased malformations (mainly fused ribs; hydronephrosis was regarded as a variation) were observed at doses of 100 mg/kg body weight and day and above. The authors derived a NOAEL for maternal toxicity of 25 mg/kg body weight and day and a NOAEL for developmental toxicity of 50 mg/kg body weight and day (Greim 1998; Schwetz et al. 1992). The Commission considers the low dose of 25 mg/kg body weight and day to be the NOAEL for developmental toxicity because litter sizes were reduced at doses of 50 mg/kg body weight and day and above.

Tab. 2 Developmental toxicity studies with diethylene glycol dimethyl ether

Species, strain, number per group		Findings	References
inhalation			
rat, Crl:CD®BR, 25–26 ♀	**GD 7–16**, 0, 25, 100, 400 ml/m³, 25 ml 2-methoxyethanol/m³, inhalation, nose-only, 6 hours/day, purity: 99%, 2-methoxyethanol: > 99%, examination: GD 21	**no NOAEC developmental toxicity** (average percentage of affected foetuses with skeletal ossifications ↑, at 25 ml/m³: incidence of rudimentary lumbar ribs already 4-fold); **25 ml/m³: NOEC maternal toxicity**; **25 ml/m³ and above**: incidence of skeletal variations ↑ (foetuses: 44/301; average percentage of affected foetuses: 17.6%; affected litters: 18/22; at 100 ml/m³: foetuses: 78/315; 24.5%; litters: 18/24; control: foetuses: 14/252; 4.5%; litters: 10/21; delayed ossification and rudimentary ribs, rudimentary lumbar ribs: foetuses: 24/301, litters: 11/22; at 100 ml/m³: foetuses: 45/315, litters: 13/24; control: foetuses: 5/252, litters: 5/21); pattern, type and incidence of variations similar to those at 100 ml/m³; values at 25 ml/m³ are therefore equivalent to the lower end of the dose–response curve; **100 ml/m³**: **NOAEC maternal toxicity**, because only marginal increase in absolute and relative liver weights; **100 ml/m³**: dams: absolute and relative liver weights ↑ (< 10%); foetuses: body weights (♀, ♂, litter) ↓; **400 ml/m³**: dams: body weights ↓ (largely because of failure to become pregnant), feed consumption ↓; 100% resorptions in all 23 pregnant dams; **25 ml 2-methoxyethanol/m³**: dams: relative liver weights ↑, feed consumption ↓; structural variations similar in incidence and severity to those induced by 25 ml DEGDME/m³; dams: no mortality; no unusual findings: number of corpora lutea/dam, number of implantations/litter; foetuses: incidence of skeletal variations: 33/281; average percentage of affected foetuses: 12.7% → similar potency	Driscoll et al. 1998; Du Pont de Nemours and Company 1988; Greim 1998
oral			
mouse, CD-1, 28 ♀	**GD 6–15**, 0, 62.5, 125, 250, 500 mg/kg body weight and day, gavage, purity: > 99%, vehicle: distilled water, examination: GD 17	**62.5 mg/kg body weight: NOAEL developmental toxicity**; **62.5 mg/kg body weight and above**: dams: gravid uterus weights ↓; live foetuses/litter ↓ (11.25 ± 0.77; 12.08 ± 0.48; 11.35 ± 0.45; 6.13 ± 0.64; controls: 13.43 ± 0.53); controls: very high number of live foetuses/litter and at 62.5 mg/kg body weight coincidental reduction in the number of implantation sites; **125 mg/kg body weight: NOAEL maternal toxicity**; **125 mg/kg body weight and above**: foetuses: body weights ↓; **250 mg/kg body weight and above**: dams: body weight gains ↓, later foetal deaths/litter ↑; post-implantation losses/litter ↑; foetuses: malformations ↑ (foetuses: 59/261; litter: 19/23); **500 mg/kg body weight**: dams: resorptions/litter ↑; foetuses: malformations (foetuses: 132/141; litter: 23/23; external: exencephaly, limbs, phalanges, craniofacial; visceral: cardiovascular, urogenital; skeletal: fused ribs and vertebral arches)	Greim 1998; Price et al. 1987
mouse, CD-1, 15 ♀, 18 ♀ controls	**GD 11**, 0, 537 mg/kg body weight, gavage, purity: 99%, vehicle: distilled water, examination: GD 18	**537 mg/kg body weight**: foetuses: malformation of the hind paws ↑ (foetuses: 77/201; 38%, litters: 13/18; 72%; syndactyly, short phalanges, oligodactyly); no maternal toxicity	Greim 1998; Hardin and Eisenmann 1987

Tab. 2 *(continued)*

Species, strain, number per group		Findings	References
mouse, CD-1, 49 ♀	**GD 6–13**, 0, 3000 mg/kg body weight and day, gavage, purity: no data, vehicle: distilled water, examination: PND 1	**3000 mg/kg body weight**: dams: mortality ↑ (20/49); 100% resorptions	Greim 1998; Hardin et al. 1987
rabbits, New Zealand White, 15–25 ♀	**GD 6–19**, 0, 25, 50, 100, 175 mg/kg body weight and day, gavage, purity: > 99%, vehicle: distilled water, examination: GD 30, according to the current OECD Test Guideline 414, treatment of the rabbit on GD 6–18	**25 mg/kg body weight: NOAEL developmental** (Commission: because of decrease in litter size at 50 mg/kg body weight and above) **and maternal toxicity**; **50 mg/kg body weight: NOAEL developmental toxicity** (authors); **50 mg/kg body weight and above**: dams: body weight gains during treatment ↓; foetuses: percentage of implantations/litter with adverse effects ↑ (resorptions, later foetal death, foetuses with malformations; individual parameters increased without statistical significance); **100 mg/kg body weight and above**: dams: gravid uterus weights ↓, percentage of prenatal mortality/litter ↑ (24.1 ± 6.9; 175 mg/kg body weight: 48.9 ± 9.0; controls: 4.1 ± 2.4), foetuses: body weights ↓, percentage of foetuses with malformations/litter ↑ (mainly fused ribs, hydronephrosis is regarded as a variation); **175 mg/kg body weight**: dams: mortality ↑	Greim 1998; Schwetz et al. 1992

DEGDME: diethylene glycol dimethyl ether; GD: gestation day; NOEC: no observed effect concentration

Manifesto (MAK value/classification)

The toxicological profile of diethylene glycol dimethyl ether is characterized by prenatal toxicity and adverse effects on fertility. The rat was found to be the most sensitive species for these effects (Greim 1998). The human data available for these end points cannot be included in the evaluation because of the exposure to a mixture of substances and the absence of exposure data.

MAK value. Male rats are more sensitive to effects on fertility than female rats. A 2-week inhalation study in rats determined a NOAEC of 30 ml/m³ for testicular damage induced by diethylene glycol dimethyl ether (Du Pont de Nemours and Company 1989; Greim 1998).

As only data from a 2-week inhalation study with diethylene glycol dimethyl ether are available and the reproductive toxicity induced by diethylene glycol dimethyl ether is attributed to the metabolite methoxyacetic acid (see Section "Mechanism of Action" and Greim 1998), the evaluation below includes also data for methoxyacetic acid and its metabolic precursor 2-methoxyethanol.

The MAK value for 2-methoxyethanol was derived using the BAT value for **methoxyethanol** of 15 mg methoxyacetic acid/g creatinine in urine. This is equivalent to a 2-methoxyethanol concentration in the air of 1.69 ml/m³. On the basis of this NOAEC in humans, the MAK value for 2-methoxyethanol has been set at 1 ml/m³ (Hartwig 2009 b).

The BAT value for 2-methoxyethanol was derived on the basis of the NOAEC for haematological effects in humans using study findings from occupational medicine (Käfferlein et al. 2016). The NOAEC for sperm toxicity in humans is in the same range (supplement "2-Methoxyethanol"; Hartwig 2009 b).

A 28-day inhalation study in rats (methoxyacetic acid concentrations of 20, 60 or 160 mg/m³) derived a NOAEC of 60 mg/m³ (15.8 ml/m³) for systemic effects and impaired fertility induced by methoxyacetic acid. After taking into

consideration a possible intensification of the effects after chronic exposure (1:6), the increased respiratory volume of the person at the workplace compared with that of animals at rest under experimental conditions (1:2) and the extrapolation of the data from the animal study to the human (1:2), this results in a concentration of 0.65 ml/m^3. However, the MAK value for methoxyacetic acid of 1 ml/m^3 was not derived from these data but in analogy to 2-methoxyethanol because more extensive data are available for this substance (supplement "Methoxyessigsäure"; Hartwig 2009 a, available in German only). The local effects were of the same order of magnitude as the systemic effects (Hartwig and MAK Commission 2018).

If the calculation is based on the NOAEC of 30 ml/m^3 derived from the findings of the 2-week inhalation study in rats for testicular damage induced by **diethylene glycol dimethyl ether** (Du Pont de Nemours and Company 1989; Greim 1998) and a possible intensification of the effects after chronic exposure (1:6), the increased respiratory volume of the person at the workplace compared with that of animals at rest under experimental conditions (1:2) and the extrapolation of the data from the animal study to the human (1:2) are taken into consideration, this results in a concentration of 1.25 ml/m^3. This value is about double that derived from the study of methoxyacetic acid in rats. The testicular toxicity induced in rats after exposure to a 2-methoxyethanol concentration of 300 ml/m^3 was more severe than that induced by diethylene glycol dimethyl ether at a concentration of 370 ml/m^3, but only slightly less severe than that induced by diethylene glycol dimethyl ether at 1100 ml/m^3 (Lee et al. 1989) (see also Section "Mechanism of Action"). On the basis of these findings it can be concluded that, after exposure to the same external concentration, the potency of diethylene glycol dimethyl ether for inducing testicular toxicity is half that of 2-methoxyethanol. This is plausible because in rats, diethylene glycol dimethyl ether (see Section "Metabolism") is not completely metabolized to 2-methoxyethanol and thus to methoxyacetic acid.

The 2-week study in rats did not cover the entire cycle of sperm development. For this reason, the NOAEC of 1.69 ml/m^3 (see above) derived from the far more extensively investigated 2-methoxyethanol is of greater relevance because it is based on the BAT value for 2-methoxyethanol and thus on human data (studies from occupational medicine). Even though the BAT value for 2-methoxyethanol was derived on the basis of haematological data, this value provides protection also against testicular toxicity. In addition, this value takes into consideration that the critical metabolite methoxyacetic acid has a longer half-life in humans than in rats. There are no data available for metabolism in humans. Therefore, the fraction of 2-methoxyethanol that forms from diethylene glycol dimethyl ether in humans is not known. Studies of developmental toxicity found that diethylene glycol dimethyl ether and 2-methoxyethanol are similar in potency at the same external concentration, which suggests that diethylene glycol dimethyl ether may be more extensively metabolized in female rats. For this reason, the MAK value for diethylene glycol dimethyl ether has been established to be 1 ml/m^3, the same MAK value as for 2-methoxyethanol.

Peak limitation. As the critical metabolite methoxyacetic acid has a long half-life (Greim 2001), exposure peaks remain limited according to Peak Limitation Category II with an excursion factor of 8.

Prenatal toxicity. Teratogenic effects were induced in mice and rabbits. In both species, a transition from skeletal variations to malformations and to intrauterine foetal death occurred with an increase in the dose (Price et al. 1987; Schwetz et al. 1992). A NOAEC cannot be derived from a prenatal developmental toxicity study in Crl:CD®BR rats with nose-only inhalation exposure. The incidence of skeletal variations was increased in foetuses at the low concentration of 25 ml/m^3 and above without concurrent maternal toxicity (Driscoll et al. 1998). In a prenatal developmental toxicity study with gavage administration in CD-1 mice, a NOAEL of 62.5 mg/kg body weight and day was derived without signs of maternal toxicity (Price et al. 1987). In a prenatal developmental toxicity study with gavage administration in New Zealand White rabbits, litter sizes were reduced at dose levels of 50 mg/kg body weight and day and above without signs of maternal toxicity (Schwetz et al. 1992). A NOAEL of 25 mg/kg body weight and day was derived from these findings.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs for developmental toxicity in mice and rabbits of 62.5 and 25 mg/kg body weight and day, respectively, to a concentration in workplace air: the corresponding species-specific correction values for the mouse and rabbit of 1:7 and 1:2.4, respectively, the

oral absorption of 90% in rats under experimental conditions (Greim 1998), the body weight of 70 kg, the respiratory volume of 10 m^3 during 8 working hours and the assumed 100% absorption by inhalation of the person. This results in concentrations of diethylene glycol dimethyl ether in air of 10 and 12 ml/m^3 (56 and 66 mg/m^3), respectively. There is a 10-fold and 12-fold margin, respectively, between these values and the MAK value of 1 ml/m^3. The margins between the concentrations in air derived from the oral studies and the derived MAK value are just adequate. However, the evaluation is based on the findings from the inhalation study because these are of greater relevance for the workplace.

Taking into consideration the increased respiratory volume (1:2), a concentration in air of 13 ml/m^3 is calculated from the LOAEC of 25 ml/m^3 that was derived from the findings of the inhalation study. This represents a 13-fold margin to the MAK value. As the incidence of foetuses with rudimentary lumbar ribs was four times higher than the incidence in the control group (Driscoll et al. 1998), the margin between the NOAEC for developmental toxicity and the MAK value is probably well below 10 and thus not adequate. A very severe effect observed at 400 ml/m^3 (equivalent to 200 ml/m^3 after taking the increased respiratory volume into consideration) was complete resorption (margin of 200 to the MAK value).

The metabolite 2-methoxyethanol, which is classified in Pregnancy Risk Group B because it has a MAK value of 1 ml/m^3, induces teratogenic effects in rats, mice and rabbits (supplement "2-Methoxyethanol"; Hartwig 2009 b). In addition, after inhalation exposure, the potency of diethylene glycol dimethyl ether for inducing skeletal variations is similar to that of 2-methoxyethanol (Driscoll et al. 1998). Of all the glycol ethers, 2-methoxyethanol/2-methoxyethyl acetate have the highest potency for inducing developmental toxicity. Their teratogenic effects decrease with increasing chain length and can quite probably be attributed to the alkoxyacetic acids that are formed (ECETOC 2005). Also, the half-life of the toxic metabolite methoxyacetic acid was found to be 77 hours in the blood of humans and thus longer than the 12 hours determined in rats (supplement "2-Methoxyethanol"; Hartwig 2009 b). Diethylene glycol dimethyl ether therefore remains classified in Pregnancy Risk Group B.

Carcinogenicity. There are still no carcinogenicity studies available. The substance is not genotoxic. Therefore, the substance has not been classified in a category for carcinogens.

Germ cell mutagenicity. No new studies of the genotoxicity induced by diethylene glycol dimethyl ether have become available since the documentation from 1994 was published (Greim 1998). Negative results were obtained in 4 mutagenicity tests in Salmonella typhimurium, a UDS test in human embryonic fibroblasts and in a chromosomal aberration test in the bone marrow cells of CD rats after 5-day inhalation exposure to concentrations up to 1000 ml/m^3. The results of a recessive lethal test in Drosophila melanogaster cannot be included in the evaluation because of an unusually high incidence of mortality in the control group. In a dominant lethal test in CD rats, the number of pre-implantation and post-implantation resorptions was increased at a concentration of 1000 ml/m^3 with a concurrent, marked impairment of male fertility and a reduced incidence of pregnancy (Greim 1998; McGregor et al. 1983). However, the dominant lethal test cannot be used for the evaluation of the end point genotoxicity because cytotoxic effects on the germ cells lead to adverse effects on fertility (Greim 1998). The data available do not support a potential for germ cell mutagenicity and therefore, the substance has not been classified in a category for germ cell mutagens.

Absorption through the skin. On the basis of the findings of an in vitro study (Section "Toxicokinetics and Metabolism"), the maximum amount dermally absorbed is estimated to be 2000 mg for humans after exposure to undiluted diethylene glycol dimethyl ether under standard conditions (2000 cm^2 surface area of skin, 1 hour of exposure). At a respiratory volume of 10 m^3 and assuming 100% absorption by inhalation, 56 mg of the substance is absorbed after exposure at the level of the MAK value. The substance is absorbed through the skin to a much greater extent and diethylene glycol dimethyl ether thus remains designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no findings of sensitizing effects in humans and no positive results were obtained in animal studies or in vitro studies. Therefore, diethylene glycol dimethyl ether has not been designated with an "Sh" or an "Sa" (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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