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2-Methoxyethanol, 2-methoxyethyl acetate, methoxyacetic acid, diethylene glycol dimethyl ether, diethylene glycol monomethyl ether – Addendum: evaluation of a pregnancy risk group for the BAT values with the parameter methoxyacetic acid

Assessment Values in Biological Material – Translation of the German version from 2024

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Keywords

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Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for prenatal toxicity and derived a methoxyacetic acid concentration in urine at which damage to the embryo or foetus is unlikely ("prerequisite for Pregnancy Risk Group C") for 2-methoxyethanol [109-86-4], 2-methoxyethyl acetate [110-49-6], methoxyacetic acid [625-45-6], diethylene glycol dimethyl ether [111-96-6], and diethylene glycol monomethyl ether [111-77-3]. These substances are classified in Pregnancy Risk Group B because adhering to the biological tolerance value (BAT value) of 15 mg methoxyacetic acid/g creatinine cannot exclude a risk to the developing foetus. This classification was based on embryo-/foetotoxic and teratogenic effects in rats, mice, rabbits and monkeys. The effects are caused by methoxyacetic acid, the metabolite of all substances. From the lowest NOAEC (no observed adverse effect concentration) for developmental toxicity in rabbits of 3 ml 2-methoxyethanol/m^3, a concentration of 0.15 ml 2-methoxyethanol/m^3 at the workplace was derived for which damage to the embryo or foetus is unlikely. This external concentration corresponds to a urine concentration of 2.5 mg methoxyacetic acid/g creatinine. Therefore, an internal exposure not higher than this concentration would be the prerequisite for an assignment to Pregnancy Risk Group C.

BAT value	**15 mg methoxyacetic acid/g creatinine** Sampling time: at the end of the shift on the last day of the working week after at least 2 weeks of exposure
Prenatal toxicity (2023)	Pregnancy Risk Group B, prerequisite for Pregnancy Risk Group C: 2.5 mg methoxyacetic acid/g creatinine

MAK value	
Methoxyacetic acid (2022)	**1 ml/m³ ≙ 3.7 mg/m³**
2-Methoxyethanol (2008)	**1 ml/m³ ≙ 3.2 mg/m³**
2-Methoxyethylacetate (2008)	**1 ml/m³ ≙ 4.9 mg/m³**
Diethylene glycol dimethyl ether (2021)	**1 ml/m³ ≙ 5.6 mg/m³**
Diethylene glycol monomethyl ether (2023)	**10 ml/m³ ≙ 50 mg/m³**
Peak limitation	Category II, excursion factor 8
Absorption through the skin	H

For the unexposed general population, the Federal Environment Agency of Germany proposed a preliminary reference value of 0.3 mg methoxyacetic acid/l urine based on the publication of Fromme et al. (2013). Additionally, HBM (human biomonitoring) values of 0.4 mg methoxyacetic acid/g creatinine (HBM I value) and 1.6 mg methoxyacetic acid/g creatinine (HBM II value) were derived in 2014 (HBM-Kommission 2014).

1 Mechanism of action

Biochemical studies indicate that methoxyacetic acid interferes with the de novo biosynthesis of purines and inhibits DNA synthesis; this is seen in connection with teratogenic effects (ECETOC 2005; Welsch 1992, 2005).

In an in vitro model of chondrogenesis, methoxyacetic acid induced apoptosis at and above 1.3×10^{-4} M in a dose-dependent manner (Scofield et al. 2006).

In vitro, methoxyacetic acid caused a statistically significant decrease in intracellular pH in mouse embryo fibroblast cells (BALB/c-3T3) and embryo stem cells (ES-D3) at 2.5 mM and above. The authors assume that the decrease in intracellular pH is one mechanism responsible for the embryotoxicity of methoxyacetic acid. At similar concentrations, ES-D3 cell differentiation to contracting cardiomyocytes was inhibited in the same study (BMC50 (benchmark concentration at which there is a 50% change compared to control): 2.9 mM (BMCL50: 2.6 mM; lower limit of the 95% confidence interval for BMC50)) (Louisse et al. 2010). In an in vitro model of embryogenesis, the total morphological score for methoxyacetic acid was 86 µg/ml (geometric mean of the three laboratories) (Piersma et al. 2008) and the BMC50 for differentiation of embryonic stem cells into contracting cardiomyocytes was 2.3–2.5 mM (de Jong et al. 2009).

Methoxyacetic acid led to a concentration-dependent increase in limb anomalies in mouse embryos of the 12th day of gestation in vitro from the lowest concentration tested of 3 mM. At and above 3 mM methoxyacetic acid, also statistically significant epigenetic modifications occurred after only one hour of incubation. At and above 10 mM, further significant effects on p53 and the biomarkers for cell cycle arrest and apoptosis were observed. 2-Methoxyethanol did not have such effects. The authors concluded that methoxyacetic acid disrupts limb development through epigenetic changes (Dayan and Hales 2014).

2 Toxikokinetics and metabolism

2.1 Humans

Seven male volunteers were exposed to 16 mg 2-methoxyethanol/m^3 (5 ml/m^3) 4 times for 50 min (10 min exposure-free intervals in between; 200 min in total) by means of a breathing mask via nose and mouth under resting conditions. Urine samples were taken after each exposure and further samples were taken during the following five days. By determining the respiratory volumes, a mean total intake of 19.4 mg of 2-methoxyethanol was obtained. For methoxyacetic acid, an elimination half-life of 77 hours was calculated (mean total recovery in urine after 24 hours: 15.3%; Groeseneken et al. 1989).

Based on the data of the study by Groeseneken et al. (1989), a simulation was carried out for the 4-week development of the urine concentrations of methoxyacetic acid after inhalation exposure to 1 ml 2-methoxyethanol/m^3 for humans (workplace exposure: 5 days/week, 8 hours/day) (SCOEL 2006). From Figure 1 (SCOEL 2006), it can be seen that the accumulation factor for the extrapolation of the excretion of methoxyacetic acid after 1 day to 2 to 4 weeks of workplace exposure is about 5.

For humans, a high dermal absorption of glycol ethers has been proven and outweighs the absorption by inhalation (55% compared with 45% (Kezić et al. 1997)).

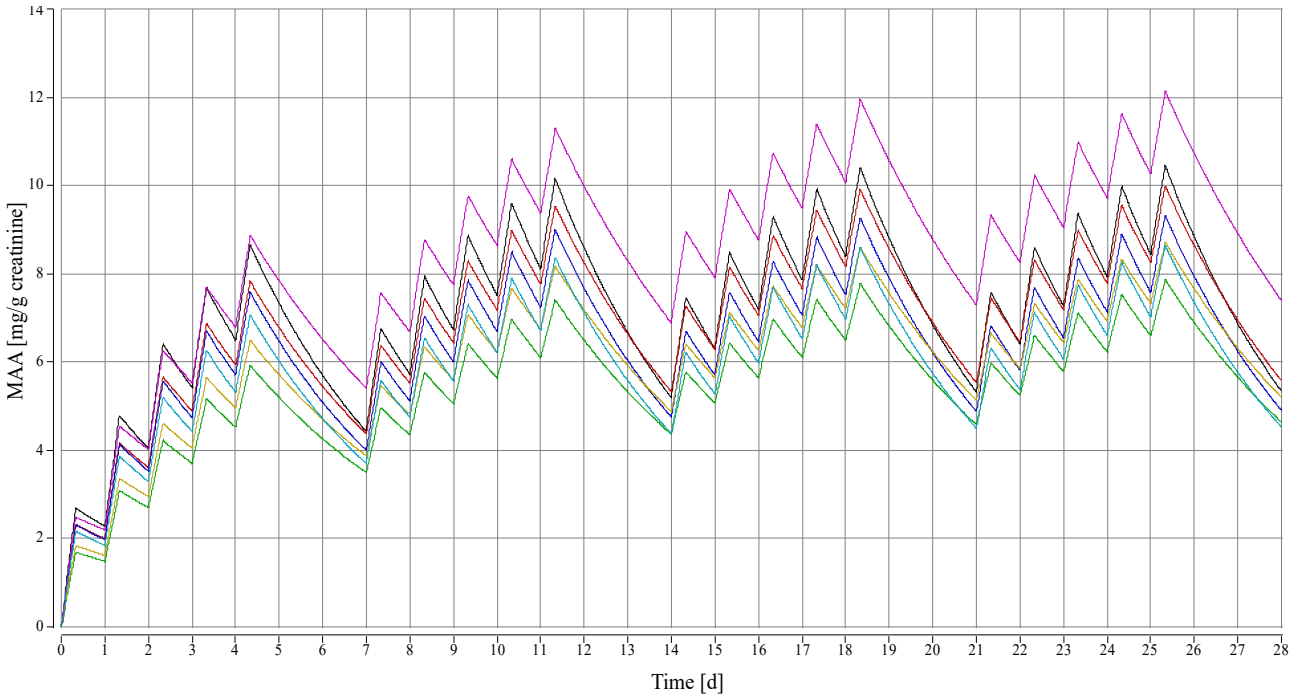

Fig. 1 Simulation of the urine concentrations of methoxyacetic acid in urine after inhalation exposure to 1 ml 2-methoxyethanol/m^3 based on the data of the volunteer study by Groeseneken et al. 1989 (SCOEL 2006, d: days, MAA: methoxyacetic acid)

2.2 Rat and mouse

Elimination half-lifes of 12 and 14 hours are reported for male and female rats, respectively (calculated from urine measurements of methoxyacetic acid after a single intraperitoneal dose of 100 mg 2-methoxyethanol/kg body weight (Aasmoe and Aarbakke 1997)).

In pregnant mice, maternal plasma concentrations of methoxyacetic acid greater than 1 mM cause developmental toxicity (Welsch et al. 1995). After exposure of pregnant rats to 10 ml (NOAEC (no observed adverse effect concentration) for developmental toxicity, rat) and 50 ml 2-methoxyethanol/m^3, the highest blood concentrations were 7.1 and 62.7 mg methoxyacetic acid/l (0.08 and 0.7 mM, respectively) (Gargas et al. 2000).

In a toxicokinetic study, blood and urine levels of methoxyacetic acid were determined in pregnant Sprague Dawley rats after inhalation (whole body exposure) of 10 and 50 ml 2-methoxyethanol/m^3 for 6 hours per day from gestation days 11 to 15. A physiologically-based pharmacokinetic model (PBPK model) was developed showing that an air concentration of 10 ml 2-methoxyethanol/m^3 in the pregnant rats corresponds to an air concentration of 12 ml 2-methoxyethanol/m^3 in humans. The model includes the extrapolation from 6 (animal experiment) to 8 hours (workplace) and the differences in the half-lives of methoxyacetic acid between rats and humans (Gargas et al. 2000).

3 Human data

Reproductive toxicity

In the supplement to the MAK value documentation for **2-methoxyethanol (**Hartwig 2009), several studies investigating the effects of occupational exposure to glycol ethers on the occurrence of congenital malformations are described, none of which, however, allow any statement to be made on possible developmental toxic effects of 2-methoxyethanol (Cordier et al. 1997, 2001; Ha et al. 1996; Shaw et al. 1999).

The Municipal Health Service of Matamoros, Mexico, identified 44 patients with congenital malformations (mainly craniofacial, musculoskeletal and central nervous system) born between April 1971 and September 1977. Their mothers were occupationally exposed to 2-methoxyethanol and ethylene glycol during their pregnancy. The exposed workers experienced severe headaches and skin rashes up to repeated vomiting and dehydration, temporary loss of consciousness and coma; in severe cases, hospital treatment was necessary (Saavedra et al. 1997). No measured data for 2-methoxyethanol are available.

As part of a clinical and cytogenetic study, 41 children of 28 female employees exposed to 2-methoxyethanol from the above-mentioned company in Matamoros, Mexico, which used 2-methoxyethanol in the production of radio and television capacitors between 1970 and 1977, were examined. The average duration of exposure for all women included in the study was 4.6 years. Five mothers of six children were exposed to 2-methoxyethanol by inhalation and dermal routes of exposure during their pregnancy; the 23 mothers of the other 35 children were not exposed during pregnancy. The six in-utero exposed children showed varying degrees of mental retardation as well as dysmorphic features and had various persistent chromosomal aberrations but no translocations or inversions. For the cytogenetic examinations, age- and sex-matched controls (12 children of unexposed mothers) were used, in which no such aberrations were detectable. The authors consider it plausible that in utero exposure to 2-methoxyethanol results in genetic instability characterised by a delay in cell division (El-Zein et al. 2002). Another study by the same research group showed that the in-utero exposed individuals had statistically significantly lower telomere lengths compared with those of the controls (El-Zein et al. 2007).

A case report from Germany describes two children with hypospadias. During both of her pregnancies, the mother was exposed to **2-methoxyethyl acetate** for at least four hours a day (1st pregnancy) and one hour a day (2nd pregnancy) during cleaning of laboratory material. One to two litres of 2-methoxyethyl acetate per day were used for cleaning (no other details). The authors discuss 2-methoxyethyl acetate as a possible cause of the congenital malformations (Bolt and Golka 1990). Information on the exposure level is not available.

Conclusion: There are several studies investigating the effects of occupational exposure to glycol ethers on the occurrence of congenital malformations, but they do not allow an assessment of possible developmental toxic effects of 2-methoxyethanol, 2-methoxyethyl acetate or methoxyacetic acid.

4 Animal findings and in vitro studies

4.1 Reproductive toxicity

4.1.1 Fertility

4.1.1.1 Male animals

For **2-methoxyethanol**, the testicular toxicity is well documented. The substance causes damage to the germinal epithelium of the testes in rats, mice and rabbits after inhalation exposure as well as after oral and dermal administration. All stages of spermatogenesis are affected. The pachytene spermatocytes (especially stages VII and VIII) represent the most sensitive phase and the phase predominantly affected by the damage. The Leydig cells, which are responsible for testosterone production, are not affected. The effect is mediated by the metabolite methoxyacetic acid (ECETOC 2005).

From a 13-week study, a NOAEC of 100 ml 2-methoxyethanol/m^3 for testicular effects (histological changes in the testes at and above 300 ml/m^3: bilateral diffuse, moderate to severe degeneration of the germinal epithelium in the seminiferous tubules) can be derived for rats and a LOAEC (lowest observed adverse effect concentration) for degenerative changes of the testes of 30 ml/m^3, but no NOAEC (no observed adverse effect concentration) for rabbits (Hartwig 2009; Miller et al. 1983). The lowest effect dose (reduced testis weights and testicular damage) after oral administration in male rats is 220 mg 2-methoxyethanol/kg body weight and day after ten days of administration with the drinking water. The NOAEL (no observed adverse effect level) is 87 mg methoxyethanol/kg body weight and day (Butterworth et al. 1995; Hartwig 2009; Johanson 2000). In male rabbits, the lowest effect dose (impaired spermatogenesis) is 25 mg 2-methoxyethanol/kg body weight and day after 12 weeks of exposure with the drinking water. The NOAEL is 12.5 mg methoxyethanol/kg body weight and day (Foote et al. 1995; Hartwig 2009; Johanson 2000).

There are no data available for **2-methoxyethyl acetate**.

Numerous studies confirm the testicular toxicity of **methoxyacetic acid**. At a dose level of 100 mg methoxyacetic acid/kg body weight and day, the first effects, such as a decreased testis weights, occurred in male rats after two weeks of oral administration. The NOAEL is 30 mg/kg body weight and day (ECETOC 2005).

For **diethylene glycol dimethyl ether** and **diethylene glycol monomethyl ether**, the testicular damage (presumably via the metabolite methoxyacetic acid) has also been shown in animal experiments. From a two-week inhalation study with **diethylene glycol dimethyl ether** in rats, a lowest inhalation effect concentration of 98 ml/m^3 was determined and a NOAEC of 30 ml/m^3 was derived (Du Pont de Nemours and Company 1989; Greim 1998; Hartwig and MAK Commission 2021). **Diethylene glycol monomethyl ether** did not cause any effects on the testis after 13 weeks of inhalation exposure in rats up to the highest concentration tested of 216 ml/m^3 (Dow Chemical Company 1984; Miller et al. 1985). However, after six weeks of oral administration at and above 1800 mg/kg body weight and day in the same species, decreased relative testis weights and, at 3600 mg/kg body weight and day, testicular atrophy and degenerated sperm in the epididymides as well as hypospermia were observed (ECETOC 2005).

4.1.1.2 Female animals

2-Methoxyethanol is toxic (presumably via the metabolite methoxyacetic acid) to the corpora lutea in the ovaries of rats. Thus, after 2 or 4 weeks of oral administration (gavage) in SD (Crl:CD(SD)) rats at and above 100 mg/kg body weight and day, there was hypertrophy of the corpora lutea, prolonged oestrus cycles (continuous dioestrus) and inhibition of ovulation. The NOAEL is 30 mg/kg body weight and day (Dodo et al. 2009; Taketa et al. 2011). A fertility study in SD (Crl:CD(SD)) rats with oral administration two weeks prior to mating, two weeks during the mating period up to gestation day 6 to females and mating with untreated males resulted in a lower mean number of implantations, a lower mean number of live embryos and an increased incidence of post-implantation loss at the dose of 100 mg/kg body weight and day (Dodo et al. 2009).

4.2 Developmental toxicity

A large number of developmental toxicity studies are available for **2-methoxyethanol**. An overview is presented in ECETOC (2005). The studies relevant for the assessment (inhalation up to 25 ml/m^3, ingestion up to 50 mg/kg body weight and day) are listed in Table 1.

2-Methoxyethanol, via the metabolite methoxyacetic acid, causes developmental toxicity, including teratogenic effects, in rats, mice, rabbits and monkeys after inhalation exposure as well as after oral and dermal application. After inhalation, the LOAECs for developmental toxicity are 25 ml 2-methoxyethanol/m^3 (rat; Driscoll et al. 1998) and 50 ml 2-methoxyethanol/m^3 (mouse; Hanley et al. 1984) and the corresponding NOAECs are 10 ml 2-methoxyethanol/m^3 (rat, mouse; Hanley et al. 1984). For the rabbit, the authors derived a NOAEC of 10 ml/m^3. At this concentration, however, statistically significantly increased rates of resorbed implantations and litters with resorptions as well as delayed ossifications of the sternum occurred. The percentage of implantations (control: 4% (7/180); 3 ml/m^3: 8% (14/186); 10 ml/m^3: 11% (23/210)* (*significantly different from control value); 50 ml/m^3: 24% (46/191)*; laboratory historical controls: 9% ± 4%; range: 4–18%) and litters with resorptions (control: 22% (5/23); 3 ml/m^3: 42% (10/24); 10 ml/m^3: 58% (14/24)*; 50 ml/m^3: 67% (16/24)*; laboratory historical controls: 39 ± 13%; range: 15–67%) are within the range of laboratory historical controls at 10 ml/m^3. The delayed ossifications (foetus base (litter base), control: 82/173 (23/23); 3 ml/m^3: 93/172 (23/23); 10 ml/m^3: 123/187 (23/24)*; 50 ml/m^3: 127/143 (22/22)*) are considered by the authors to be within the range of "normal" variability of this species without further specification (Hanley et al. 1984). In the Commission's view, this is a borderline case. As effects cannot be excluded at 10 ml/m^3, no maternal toxicity occurred and the substance belongs to a known group of teratogenic substances, the NOAEC for developmental toxicity for the rabbit in this study is conservatively set at 3 ml/m^3 (LOAEC 10 ml/m^3).

The LOAELs (lowest observed adverse effect levels) for developmental toxicity after oral administration are 25 and 31 mg 2-methoxyethanol/kg body weight and day (rat and mouse, respectively; Nagano et al. 1981; Nelson et al. 1989; Toraason et al. 1985) and 12 mg 2-methoxyethanol/kg body weight and day (monkey; Scott et al. 1989). For rats, the oral NOAEL for teratogenicity is 16 mg 2-methoxyethanol/kg body weight and day (Nelson et al. 1989), while an overall NOAEL for developmental toxicity cannot be derived for the mouse and monkey species (Table 4.1.3 in ECETOC 2005; Nagano et al. 1981; Scott et al. 1989). No developmental toxicity studies with oral exposure are available for rabbits. In long-term studies on reproductive toxicity (Reproductive Assessment by Continuous Breeding) in rats, a NOAEL of about 15 mg 2-methoxyethanol/kg body weight and day was found after drinking water administration, if the 2nd generation was produced with the 5th litter of the 1st generation. However, if the 2nd litter was used to generate the 2nd generation, a NOAEL could not be derived due to a reduced number of live offspring in the F1 generation (Gulati et al. 1991; NTP 1990 a, b). However, it should be noted that foetotoxicity may interfere with fertility due to the effects of 2-methoxyethanol on in-utero development and paternal testes/sperms (ECETOC 2005). In Wistar rats, after dermal occlusive application from days 6 to 15 of gestation, increased malformations, embryotoxicity and foetotoxicity occurred even at the lowest dose of 50 mg 2-methoxyethanol/kg body weight and day and above. A NOAEL could not be derived (Hellwig 1993 cited in ECETOC 2005). This unpublished study report was not available.

There is only one pre-study on developmental toxicity for **2-methoxyethyl acetate**. Forty-nine pregnant CD-1 mice were given gavage doses of 1225 mg 2-methoxyethyl acetate/kg body weight and day from days 6 to 13 of gestation. The evaluation was performed according to the Chernoff-Kavlock protocol. No deaths occurred in the dams. No live foetus was present in 31 litters (Hardin et al. 1987). As 2-methoxyethyl acetate is rapidly hydrolysed to 2-methoxyethanol, a teratogenic potential is likewise assumed for this substance (ECETOC 2005; Henschler 1984).

Few studies are available on **methoxyacetic acid**, which, however, prove its strong developmental toxicity and especially teratogenic potential. However, the dose at which teratogenic effects occur is not known; presumably at lower doses/concentrations compared to 2-methoxyethanol (ECETOC 2005).

In Wistar rats, after oral administration on gestational day 12, methoxyacetic acid and 2-methoxyethanol on an equimolar basis have been shown to be similarly potent in inducing heart, tail and limb defects and hydronephrosis. Thus, the proportion of foetuses with limb defects is 9.3% at 2.07 mmol (158 mg/kg body weight) 2-methoxyethanol and 60.6% at 4.14 mmol (315 mg/kg body weight) 2-methoxyethanol. After administration of 2.07 mmol (190 mg/kg body

weight) and 4.14 mmol (380 mg/kg body weight) methoxyacetic acid, the proportions are 14.4% and 69.1%, respectively (Ritter et al. 1985).

Developmental toxicity and, in particular, teratogenicity have also been shown in animal experiments for **diethylene glycol dimethyl ether** and **diethylene glycol monomethyl ether**. After nose-only inhalation, an increased incidence of foetal skeletal variations without maternal toxicity is the main effect of **diethylene glycol dimethyl ether** in rats at 25 ml/m^3 and above. At 400 ml/m^3, already 100% resorptions were observed (Driscoll et al. 1998). In mice and rabbits, the transition from skeletal variations to malformations and intrauterine foetal death becomes obvious with increasing doses of diethylene glycol dimethyl ether after gavage administration (Hartwig and MAK Commission 2021; Price et al. 1987; Schwetz et al. 1992). The lowest effect doses are 125 mg/kg body weight and day in mice (NOAEL 62.5 mg/kg body weight and day; Hartwig and MAK Commission 2021; Price et al. 1987) and 50 mg/kg body weight and day in rabbits (NOAEL 25 mg/kg body weight and day; Hartwig and MAK Commission 2021; Schwetz et al. 1992). In a prenatal developmental toxicity study in rats, **diethylene glycol monomethyl ether** led to decreased body weights, reduced ossification of the sternebrae and vertebrae, and visceral variations in the foetus after gavage doses of 600 mg/kg body weight and day without maternal toxicity (Yamano et al. 1993). With increasing doses, skeletal variations and malformations of the vertebrae and ribs as well as visceral variations and malformations, especially of the cardiovascular system, occurred more frequently in this species (Hardin et al. 1986; Yamano et al. 1993). The NOAEL for developmental toxicity is 200 mg/kg body weight and day (Yamano et al. 1993).

Tab. 1 Developmental toxicity studies relevant for assessment after administration of 2-methoxyethanol

Species, strain, number per group	Exposure	Findings	References
Inhalation[a)]			
rat, F344, 30–31 ♀	**GD 6–15**, 0, 3, 10, 50 ml/m^3, 6 hours/day, examination on GD 21, **similar to OECD TG 414**	**no NOAEC for maternal toxicity**; **3 ml/m^3 and above**: dams: haemoglobin ↓, haematocrit ↓; **10 ml/m^3: NOAEC for developmental toxicity**; **50 ml/m^3**: dams: erythrocyte count ↓, absolute liver weights ↑; foetuses: skeletal variations ↑	Hanley et al. 1984
rat, Crl:CD BR, 25–26 ♀	**GD 7–16**, 0, 25 ml/m^3, used as positive control, 6 hours/day, nose-only, examination on GD 22	**25 ml/m^3**: dams: relative liver weight ↑, food consumption ↓; foetuses: delayed ossifications (cranial bones, especially interparietal, parietal, supraoccipital), skeletal variations ↑ (rudimentary lumbar ribs)	Driscoll et al. 1998
mouse, CF-1, 30–32 ♀	**GD 6–15**, 0, 10, 50 ml/m^3, 6 hours/day, examination on GD 18, **similar to OECD TG 414** (one concentration less)	**10 ml/m^3: NOAEC for developmental and maternal toxicity**; **50 ml/m^3**: dams: body weight gains ↓; foetuses: skeletal variations ↑, unilateral testicular hypoplasia ↑	Hanley et al. 1984

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rabbits, New Zealand White, 29–30 ♀	**GD 6–18**, 0, 3, 10, 50 ml/m³, 6 hours/day, examination on GD 29, **similar to OECD TG 414**	**3 ml/m³: NOAEC for developmental toxicity (see text)**; **10 ml/m³: NOAEC for developmental toxicity according to the authors; NOAEC for maternal toxicity**; **10 ml/m³ and above**: foetuses: resorptions ↑ (control: 4% (7/180); 3 ml/m³: 8% (14/186); 10 ml/m³: 11% (23/210)*; 50 ml/m³: 24% (46/191)*; laboratory historical controls: 9% ± 4%; range: 4–18%), percentage of litters with resorptions ↑ (control: 22% (5/23); 3 ml/m³: 42% (10/24); 10 ml/m³: 58% (14/24)*; 50 ml/m³: 67% (16/24)*; laboratory historical controls: 39% ± 13%; range: 15–67%), reduced ossification of the sternebrae: foetus base (litter base) (control: 82/173 (23/23); 3 ml/m³: 93/172 (23/23); 10 ml/m³: 123/187 (23/24)*; 50 ml/m³: 127/143 (22/22)*); **50 ml/m³**: dams: body weight gains ↓ (with body weight being increased in a statistically significant manner on GD 6), absolute liver weights ↑; foetuses: body weight ↓, visceral malformations ↑ (particularly affected: heart, spleen, kidney), skeletal malformations ↑, skeletal and visceral variations ↑	Hanley et al. 1984
Oral			
rat, Sprague Dawley, 9–12 ♀	**GD 7–18**, 0, 0.006, 0.012, 0.025, 0.05, 0.1, 0.25, 0.5% in liquid food (0, 16, 31, 73, 140, 198, 290, 620 mg/kg body weight and day), liquid food, examination on GD 20, **similar to OECD TG 414** (smaller number of animals, more dose levels, individual variations or malformations not shown, only total number)	**16 mg/kg body weight: NOAEL for teratogenicity**; **16 mg/kg body weight and above**: foetuses: body weights ↓ (not related to litter); **31 mg/kg body weight: NOAEL for maternal toxicity;** **31 mg/kg body weight and above**: foetuses: visceral and skeletal malformations ↑ (double and/or misplaced aortas and/or ventricular septal defects; fused ribs, missing vertebrae); **140 mg/kg body weight and above**: dams: body weight gain ↓; foetuses: 100% mortality	Nelson et al. 1989
rat, Sprague Dawley, dosed groups: 8 ♀, control group: 11 ♀	**GD 7–13**, 0, 25, 50, 100 mg/kg body weight and day, gavage, examination on GD 20, focus on heart examination	**no NOAEL for developmental toxicity**; **25 mg/kg body weight**: foetuses: ECG: prolonged QRS wave (indication of intraventricular conduction disturbance); **50 mg/kg body weight**: **NOAEL for maternal toxicity**; foetuses: cardiovascular malformations ↑ (mainly ventricular septal defects and right ductus arteriosus); **100 mg/kg body weight**: dams: 100% resorptions	Toraason et al. 1985

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, VAF Crl: CD BR outbred Sprague Dawley, dosed groups: 20 ♀ and 20 ♂, control group: 40 ♀ and 40 ♂	**Reproductive Assessment by Continous Breeding (RACB)**, 2 generations, exposure for about 20 weeks; development of a protocol for rats; to generate the 2nd generation: 2nd litter of the 1st generation used: 0, 0.01, 0.03, 0.1% in the drinking water (0; F0: ♀: 12.7, 36.3, 122.1 mg/kg body weight and day, ♂: 8.8, 23.6, 75.8 mg/kg body weight and day; F1: ♀: 15.0, 40.8 mg/kg body weight and day, ♂: 9.1, 27.2 mg/kg body weight and day); for the generation of the 2nd generation: 5th litter of the 1st generation used: 0, 0.006, 0.012, 0.024% in the drinking water (0; F0: ♀: 7.3, 15.3, 32.7 mg/kg body weight and day, ♂: 5.0, 9.6, 20.9 mg/kg body weight and day; F1: ♀: 7.1, 14.2, 24.6 mg/kg body weight and day, ♂: 3.9, 8.1, 15.6 mg/kg body weight and day)	2nd litter: **0.01%**: F1: number of live offspring ↓; **0.03%**: F0: number of live offspring/litter ↓ (♂, ♀, combined); **0.1%**: F0: fertility index ↓ (5%, control: 100%); 5th litter: **0.012%: NOAEL (F0 ♀: 15.3; F1 ♀: 14.2 mg/kg body weight);** **0.024%**: F0, F1: number of live offspring/litter ↓; foetotoxicity can interfere with fertility (ECETOC 2005): see Section 4.1.1 (marked testicular toxicity)	Gulati et al. 1991; NTP 1990 a, b
mouse, ICR, 21–24 ♀	**GD 7–14**, 0, 31, 63, 125, 250, 500, 1000 mg/kg body weight and day, gavage, vehicle: deionised water, examination on GD 18, focus on external and skeletal examination	**no NOAEL for developmental toxicity**; **31 mg/kg body weight and above**: foetuses: skeletal variations ↑ (bifurcated or split cervical spine); **125 mg/kg body weight: NOAEL for maternal toxicity**; **125 mg/kg body weight and above**: foetuses: body weight ↓; **250 mg/kg body weight and above**: dams: body weight gain ↓; foetuses: mortality ↑, external malformations (exencephaly, oligodactyly, umbilical hernias), skeletal malformations (fused ribs, fused or missing vertebrae, spina bifida occulta); **500 mg/kg body weight**: foetuses: only one living foetus (with exencephaly, malformed digits); **1000 mg/kg body weight**: dams: leukopenia, foetuses: 100% mortality	Nagano et al. 1981
monkey, Macaca fascicularis, dose groups: 8–14 ♀, control group: 6 ♀, ethanol group: 3 ♀	**GD 20–45**, 0, 12, 24, 36 mg/kg body weight and day, gavage, vehicle: water, control groups: group 1: without gavage treatment, group 2: gavage with the corresponding ethanol volume, examination on GD 100	**no NOAEL for developmental and maternal toxicity**; **12 mg/kg body weight and above**: dams: mild anorexia; **12 mg/kg body weight**: foetuses: 4/14 intrauterine death; **24 mg/kg body weight**: dams: anorexia and therefore gavage with gruel and/or electrolytes, foetuses: 3/11 intrauterine death (of which 1 spontaneous abortion); **36 mg/kg body weight**: dams: severe anorexia and therefore gavage with gruel and/or electrolytes, foetuses: 8/8 intrauterine death, one foetus with external malformations (lack of one digit on each forelimb); Half-life of methoxyacetic acid in maternal serum approx. 20 hours	Scott et al. 1989

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
Dermal			
rat, Wistar, 45–50 ♀	**GD 6–15**, 0, 50, 100, 290, 480, 770, 970 mg/kg body weight and day, occlusive, 6 hours/day, examination on GD 20, **presumably similar to OECD TG 414**	**no NOAEL for developmental toxicity**; **50 mg/kg body weight**: foetuses: malformations ↑, foeto- and embryotoxicity; **100 mg/kg body weight**: dams: body weight gain ↓, postimplantation loss (26.5%); foetuses: malformations ↑; **290 mg/kg body weight**: dams: postimplantation loss (99.4%); foetuses: 5 malformed foetuses; **480 mg/kg body weight and above**: dams: body weights ↓, no litters, resorptions 100%	Hellwig 1993 cited in ECETOC 2005 study report not available

[a)]whole body exposure if not mentioned otherwise
ECG: electrocardiogram; GD: gestation day; TG: Test Guideline

Conclusion: Among the glycol ethers, 2-methoxyethanol and 2-methoxyethyl acetate have the highest developmental toxicity potency. The effect is mediated by the metabolite methoxyacetic acid. Teratogenic effects affect the skeleton and internal organs, with the focus on malformations of the ribs and vertebral bodies and cardiovascular malformations. At higher doses, intrauterine death of embryos/foetuses occurs. The NOAECs/NOAELs and LOAECs/LOAELs for developmental toxicity in rats, mice, rabbits and monkeys after administration of 2-methoxyethanol are shown in Table 2.

Tab. 2 Assessment-relevant NOAEC/L and LOAEC/L for developmental toxicity after administration of 2-methoxyethanol

Species, end point, administration	NOAEC/NOAEL	LOAEC/LOAEL	References
rat			
prenatal, inhalation	10 ml/m³	50 ml/m³	Hanley et al. 1984
prenatal, inhalation	–	25 ml/m³	Driscoll et al. 1998
prenatal, oral	16 mg/kg body weight and day	25 and 31 mg/kg body weight and day	Nelson et al. 1989; Toraason et al. 1985
prenatal, dermal occlusive	–	50 mg/kg body weight and day	ECETOC 2005
mouse			
prenatal, inhalation	10 ml/m³	50 ml/m³	Hanley et al. 1984
prenatal, oral	–	31 mg/kg body weight and day	Nagano et al. 1981
rabbit			
prenatal, inhalation	3 ml/m³	10 ml/m³	Hanley et al. 1984
monkey (macaque)			
prenatal, oral	–	12 mg/kg body weight and day	Scott et al. 1989

5 Assessment

Prenatal toxicity

Human data

There are several studies investigating the effects of occupational exposure to glycol ethers on the occurrence of congenital malformations, but they do not allow any concrete statement on possible developmental toxic effects of 2-methoxyethanol, 2-methoxyethylacetate or methoxyacetic acid.

Animal data

Among the glycol ethers, 2-methoxyethanol and 2-methoxyethyl acetate have the highest developmental toxicity potency. The effect is mediated by the metabolite methoxyacetic acid. Teratogenic effects affect the skeleton and internal organs, with the focus on malformations of the ribs and vertebral bodies and cardiovascular malformations. At higher doses, intrauterine death of embryos/foetuses occurs. The NOAEC/NOAEL and LOAEC/LOAEL for developmental toxicity in rat, mouse, rabbit and monkey relevant for the assessment are shown in Table 2. The NOAEC for developmental toxicity in the rat is 10 ml 2-methoxyethanol/m^3 and in the rabbit 3 ml 2-methoxyethanol/m^3. After oral administration, a NOAEL for developmental toxicity of 16 mg/kg body weight and day could be derived only for the rat.

Assignment to a pregnancy risk group

There are insufficient margins between the MAK value for 2-methoxyethanol of 1 ml/m^3 and the NOAEC for developmental toxicity (see above). The MAK value for 2-methoxyethanol was derived in 2008 via a regression line from field studies in correlation to the BAT value of 15 mg methoxyacetic acid/g creatinine (Hartwig 2009). As the MAK value for 2-methoxyethanol is assigned to Pregnancy Risk Group B, the correlative derivation allows the assignment to Pregnancy Risk Group B to be transferred to the BAT value of 15 mg methoxyacetic acid/g creatinine.

Indication of prerequisite for Pregnancy Risk Group C

For the situation at the workplace, the inhalation studies are most relevant. Therefore, the NOAECs for developmental toxicity in the rat of 10 ml 2-methoxyethanol/m^3 and in the rabbit of 3 ml 2-methoxyethanol/m^3 are used as a starting point. For the extrapolation to the human situation at the workplace, the PBPK model of Gargas et al. (2000) is used (10 ml 2-methoxyethanol/m^3 in the pregnant rat corresponds to 12 ml 2-methoxyethanol/m^3 for 8-hour exclusive exposure by inhalation in humans). In addition, the dermal absorption from the gaseous phase, which is about as high as the absorption by inhalation, and the increased respiratory volume have to be taken into account (volunteer study with mask inhalation at rest). As the factor for the increased respiratory volume (1:2) also comprises the extrapolation of 6 hours exposure in the animal experiment to 8 hours exposure at the workplace, but the PBPK model already contains this extrapolation, a factor of 0.66 results for the increased respiratory volume (1:1.5; Hartwig and MAK Commission 2017). From this, an air concentration c of 4.77 ml 2-methoxyethanol/m^3 (c/0.66 + c = 12 ml/m^3) is calculated, taking into account inhalation and dermal absorption. There is no PBPK model for the rabbit, so from the NOAEC of 3 ml/m^3, taking into consideration the 6-hour exposure and the increased respiratory volume (1:2), an air concentration of 1.5 ml 2-methoxyethanol/m^3 is obtained. The dermal absorption from the gaseous phase is already included, as the animals were exposed whole-body and it is assumed that the dermal absorption in rabbits and humans is the same. Based on the calculated air concentrations of 4.77 ml/m^3 from the experiment with rats and of 1.5 ml/m^3 from that with rabbits, it follows that at a margin of 10, i. e. **0.47 and 0.15 ml/m^3** respectively, damage to the embryo and foetus caused by 2-methoxyethanol is unlikely.

The conversion of the air concentrations of 2-methoxyethanol into urine concentrations of methoxyacetic acid is based on the data of the volunteer study by Groeseneken et al. (1989) after exposure to 5 ml of 2-methoxyethanol/m^3 (via breathing mask at rest). The exposure of 4 times 50 min (200 min) corresponds to a mean total absorption of

19.4 mg of 2-methoxyethanol, of which 15.3% (approx. 3 mg) are excreted as methoxyacetic acid after 24 hours (see Section 2.1). Extrapolated to an 8-hour exposure, this corresponds to 7.2 mg methoxyacetic acid (3 mg methoxyacetic acid × 480 min/200 min). Taking into consideration that the same amount is additionally absorbed via the skin and via the increased respiratory volume (3 × 7,2 mg, 21.6 mg in total) results in an excretion of 7.2 mg methoxyacetic acid (21.6 mg methoxyacetic acid × 8/24) after 8 hours of exposure. Converted to creatinine, this results in an excretion of 16.7 mg methoxyacetic acid/g creatinine, as creatinine excretion is 1.3 g/24 hours (Weihrauch et al. 1999) (in 8 hours correspondingly 0.43 g creatinine; 7.2 mg methoxyacetic acid/0.43 g creatinine). Including the factor of 5 for extrapolation from 8 hours to the steady state (see Section 2.1) leads to a concentration of 83.5 mg methoxyacetic acid/g creatinine (5 × 16.7 mg methoxyacetic acid/g creatinine) after a repeated 8-hour exposure to 5 ml 2-methoxyethanol/m^3. A repeated 8-hour exposure to 1 ml 2-methoxyethanol/m^3 therefore corresponds to a urine concentration of 16.7 mg methoxyacetic acid/g creatinine in the steady state.

The calculated air concentrations of 0.47 (rat) and 0.15 (rabbit) ml 2-methoxyethanol/m^3 thus correspond to **7.8 and 2.5 mg methoxyacetic acid/g creatinine**, respectively.

From the data and toxicokinetic calculations described, it can be concluded that up to a urine concentration of 2.5 mg methoxyacetic acid/g creatinine, damage to the embryo/foetus is not to be expected.

As the developmental toxicity is mediated by methoxyacetic acid, the prerequisite for Pregnancy Risk Group C is a urine concentration of 2.5 mg methoxyacetic acid/g creatinine for 2-methoxyethanol, 2-methoxyethyl acetate, methoxyacetic acid, diethylene glycol dimethyl ether and diethylene glycol monomethyl ether for which a BAT value for the parameter methoxyacetic acid was derived.

It should be noted that due to accumulation, the determinations of methoxyacetic acid in the urine should be carried out at the end of the shift on the last day of the working week after at least 2 weeks of exposure.

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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