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Diethylene glycol dimethyl ether – Evaluation of a BAT value

Assessment Values in Biological Material – Translation of the German version from 2022

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Keywords

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Abstract

In 2019, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has derived a maximum workplace concentration (MAK value) of 1 ml/m^3 (5.56 mg/m^3) for diethylene glycol dimethyl ether (DEGDME) [111-96-6].

Data of the DEGDME metabolism in humans are not available. In rats, DEGDME is metabolised to methoxyethoxyacetic acid as well as methoxyacetic acid. The toxic effect of DEGDME is caused by the metabolite methoxyacetic acid and its metabolic precursor 2-methoxyethanol (ethylene glycol monomethyl ether). Therefore, those metabolites were considered for the derivation of a biological tolerance value (BAT value).

The BAT value for 2-methoxyethanol of 15 mg methoxyacetic acid/g creatinine was based on the NOAEC (no observed adverse effect concentration) of the effects on the erythropoetic system (haematotoxicity) in humans. The NOAEC of testicular toxicity is in the same order of magnitude. The compliance with the BAT value of 15 mg methoxyacetic acid/g creatinine (that is, keeping the exposure levels below these values) is intended to protect the health of persons exposed to DEGDME. Therefore, a BAT value of 15 mg methoxyacetic acid/g creatinine was derived for DEGDME. Sampling time is at the end of shift, for long-term exposure after several previous shifts.

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BAT value (2021)	**15 mg methoxyacetic acid/g creatinine** Sampling time: end of exposure or end of shift; at the end of the shift, for long-term exposures after several previous shifts
MAK value (2020)	**1 ml/m³ ≙ 5.56 mg/m³**
Absorption through the skin (1994)	H
Carcinogenicity	–
Prenatal toxicity (1994)	Pregnancy Risk Group B
Synonyms	bis(2-methoxyethyl) ether DEGDME diglyme 1-methoxy-2-(2-methoxyethoxy)ethane 1,1′-oxybis(2-methoxyethane)

Diethylene glycol dimethyl ether (DEGDME, [111-96-6]) is a solvent used in various applications such as organic synthesis, as an additive in brake and hydraulic fluids and in dispersion paints, for the production of polyurethane varnishes, textile dyes and as a solvent in the semiconductor industry (IKSR 2013).

In 1994, the Commission derived a maximum workplace concentration (MAK value) of 5 ml DEGDME/m³ (28 mg DEGDME/m³) (translated in Greim 1998), which was lowered to 1 ml DEGDME/m³ (5.56 mg DEGDME/m³) in 2020 (Hartwig and MAK Commission 2021).

1 Metabolism

In rats, it was shown that there are two metabolic pathways of DEGDME. After a single DEGDME dose, metabolism takes place preferentially via O-demethylation to 2-methoxyethoxyethanol. After repeated administration of DEGDME, there is an increase in oxidative cleavage of the central ether bond after enzyme induction, leading to the formation of the metabolite methoxyacetic acid. When DEGDME was administered orally once to rats, the main metabolite was methoxyethoxyacetic acid (68% of the dose) followed by methoxyacetic acid (6.2% of the dose). After repeated administration, the proportion of 2-methoxyethoxyacetic acid remained the same, but 10% was excreted as methoxyacetic acid (Hartwig and MAK Commission 2021) (Figure 1). Metabolism studies on DEGDME in humans are not available.

2 Toxic Effects and Mode of Action

DEGDME is highly volatile and its acute toxicity is low.

With regard to chronic toxicity, the haematotoxic, teratogenic and reproductive effects are of importance. Repeated administration in animal experiments in various species caused toxic effects mainly on the haematopoietic and lymphoid organs, testicular germinal epithelium as well as embryonic and foetal tissues in utero. The main characteristics of the effect of DEGDME are therefore testicular toxicity, such as atrophy of the testes and epididymides, degeneration of germ cells and disruption of spermatogenesis, as well as embryotoxic or foetotoxic and teratogenic effects (Greim 1998). As they cannot be excluded when exposed to DEGDME at the level of the MAK value, the substance was assigned to Pregnancy Risk Group B.

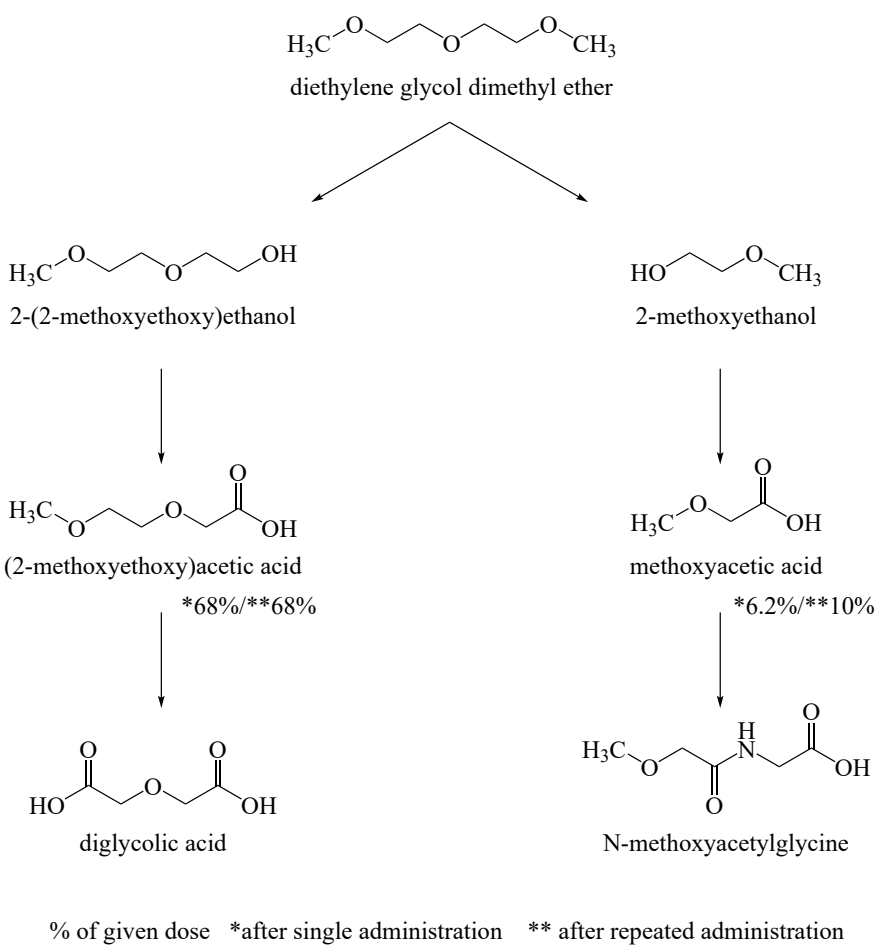

Fig. 1 Metabolism of diethylene glycol dimethyl ether in male rats after oral administration (translated from Hartwig and MAK Commission 2021, according to Cheever et al. 1988).

The metabolites 2-methoxyethanol and methoxyacetic acid are responsible for the reproductive toxicity. Neither testicular damage nor teratogenic effects were observed with the DEGDME metabolite methoxyethoxyacetic acid or its metabolic precursor 2-methoxyethoxyethanol. Foetotoxic effects were observed with 2-methoxyethoxyethanol only at high doses with simultaneous maternal toxicity. In contrast, 2-methoxyethanol, like DEGDME, caused foetotoxic effects in the rat with no effects on the dams (NOAEC (no observed adverse effect concentration) 10 ml/m^3). Repeated exposure to DEGDME leads to an increased cleavage of the central ether bond and thus to the increased formation of 2-methoxyethanol or methoxyacetic acid (Greim 1998; Hartwig and MAK Commission 2021).

3 Analytical Methods

The determination of methoxyacetic acid and other alkoxycarboxylic acids in urine by gas chromatography-mass spectrometry (GC-MS) has been published as a reliable and proven method by the Commission's Working Group "Analyses in Biological Materials" (Göen et al. 2006).

Furthermore, the working group has tested a method for the determination of propylene and diethylene glycol ethers in urine by means of capillary gas chromatography with flame ionisation detector (GC-FID). This method can also be used to analyse DEGDME (Angerer et al. 2008).

4 Evaluation of a BAT value

Since the toxic effects of DEGDME are attributed to the metabolite methoxyacetic acid (Hartwig and MAK Commission 2021), in addition to methoxyacetic acid also the metabolic precursor 2-methoxyethanol is considered in the following for the derivation of a BAT value (biological tolerance value). From studies in rats it is known that DEGDME is metabolised to 2-methoxyethanol and further to methoxyacetic acid (6–10%) (Hartwig and MAK Commission 2021).

The BAT value for 2-methoxyethanol of 15 mg methoxyacetic acid/g creatinine is derived from the NOAEC for haematological effects in humans obtained from occupational health studies (translated in Käfferlein et al. 2016). The NOAEC for testicular toxicity in humans is in a similar order of magnitude (Hartwig and MAK Commission 2021). Compliance with this BAT value for 2-methoxyethanol protects against toxic effects from exposure to DEGDME.

Based on these findings,

a BAT value for DEGDME of 15 mg methoxyacetic acid/g creatinine

has been set.

Due to the long half-life of methoxyacetic acid of about 70 hours, accumulation over the working week is to be expected. Sampling should therefore be carried out at the end of the shift, after several previous shifts at the end of the working week.

5 Interpretation

The BAT value relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l (Bader et al. 2016). As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended.

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.

References

Angerer J, Göen T, Hubner B, Weiß T, Blaszkewicz M, Aust B (2008) Propylene and diethylene glycol ethers. Biomonitoring Method, 2008. In: Angerer J, Hartwig A, editors. The MAK-Collection for Occupational Health and Safety. Part IV: Biomonitoring Methods. Volume 11. Weinheim: Wiley-VCH. p. 231–260. Also available from https://doi.org/10.1002/3527600418.bi10798e0011

Bader M, Ochsmann E, Drexler H, Hartwig A, MAK Commission (2016) Addendum to creatinine as reference parameter for the concentration of substances in urine. BAT Value Documentation, 2010. MAK Collect Occup Health Saf 1(1): 266–268. https://doi.org/10.1002/3527600418.bbgeneral05e1715

Cheever KL, Richards DE, Weigel WW, Lal JB, Dinsmore AM, Daniel FB (1988) Metabolism of bis(2-methoxyethyl) ether in the adult male rat: evaluation of the principal metabolite as a testicular toxicant. Toxicol Appl Pharmacol 94(1): 150–159. https://doi.org/10.1016/0041-008x(88)90345-6

Göen T, Bader M, Müller G (2006) Alkoxycarboxylic acids in urine as metabolites of glycol ethers with a primary alcohol group. Biomonitoring Method, 2006. In: Angerer J, Greim H, editors. The MAK-Collection for Occupational Health and Safety. Part IV: Biomonitoring Methods. Volume 10. Weinheim: Wiley-VCH. p. 55–80. Also available from https://doi.org/10.1002/3527600418.bi62545e0010

Greim H, editor (1998) Diethylene glycol dimethyl ether. MAK Value Documentation, 1994. In: Occupational Toxicants. Volume 9. Weinheim: Wiley-VCH. p. 41–50. Also available from https://doi.org/10.1002/3527600418.mb11196e0009

Hartwig A, MAK Commission (2021) Diethylenglykoldimethylether. MAK-Begründung, Nachtrag. MAK Collect Occup Health Saf 6(1): Doc003. https://doi.org/10.34865/mb11196d6_1ad

IKSR (Internationale Kommission zum Schutz des Rheins) (2013) Auswertungsbericht Industriechemikalien. Fachbericht Nr. 202. Koblenz: IKSR. https://www.iksr.org/fileadmin/user_upload/DKDM/Dokumente/Fachberichte/DE/rp_De_0202.pdf, accessed 30 Mar 2022

Käfferlein H, Drexler H, Hartwig A, MAK Commission (2016) Ethylene glycol monomethyl ether and ethylene glycol monomethyl ether acetate. BAT Value Documentation, 2009. MAK Collect Occup Health Saf 1(2): 1207–1223. https://doi.org/10.1002/3527600418.bb10986e1615