The MAK Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Diethylene glycol monomethyl ether – Evaluation of a BAT Value

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

K. Klotz[1]
H. Drexler[2,*]
A. Hartwig[3,*]
MAK Commission[4,*]

1 *Employer's liability insurance association for wood and metal, Weinmarkt 9–11, 90403 Nürnberg, Germany*

2 *Head of the working group "Assessment Values in Biological Material" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine, Henkestraße 9–11, 91054 Erlangen, Germany*

3 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

4 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

diethylene glycol monomethyl ether; methoxyacetic acid; biological tolerance value; BAT value

Abstract

In 2023, the German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) derived an occupational exposure limit value (maximum concentration at the workplace, MAK value) of 10 ml/m^3 (50 mg/m^3) for diethylene glycol monomethyl ether [111-77-3]. In this article, the data for diethylene glycol monomethyl ether are summarized and evaluated to derive a biological tolerance value (BAT value). The toxic effect of diethylene glycol monomethyl ether is related to the metabolite methoxyacetic acid and its metabolic precursor 2-methoxyethanol (ethylene glycol monomethyl ether). Therefore, those metabolites were considered for the evaluation of the BAT value. The BAT value for 2-methoxyethanol of 15 mg methoxyacetic acid/g creatinine was derived from the no observed adverse effect concentration (NOAEC) for haematotoxicity in humans. The NOAEC of testicular toxicity is in the same order of magnitude. Therefore, a BAT value of 15 mg methoxyacetic acid/g creatinine was derived for diethylene glycol monomethyl ether. Sampling time is at the end of the shift on the last day of the working week after at least 2 weeks of exposure.

Citation Note:
Klotz K, Drexler H, Hartwig A, MAK Commission. Diethylene glycol monomethyl ether – Evaluation of a BAT Value. Assessment Values in Biological Material – Translation of the German version from 2024. MAK Collect Occup Health Saf. 2024 Mar;9(1):Doc018. https://doi.org/10.34865/bb11177e9_1or

Manuscript completed:
01 Apr 2022

Publication date:
28 Mar 2024

BAT value (2023)	**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 (2023)	**10 ml/m³ ≙ 50 mg/m³**
Absorption through the skin (2023)	H
Carcinogenicity	–
Synonyms	DEGME Diethylene glycol methyl ether Diglycol monomethyl ether 2-(2-Methoxyethoxy)ethanol 2-(2-Methoxyethoxy)ethan-1-ol Methyldiglycol
Structural formula	$HO\text{-}(CH_2)_2\text{–}O\text{–}(CH_2)_2\text{-}O\text{-}CH_3$

The main application of diethylene glycol monomethyl ether is as an antifreeze in aviation fuel. It is also used as a chemical intermediate in synthesis, as a solvent in paints and floor polishes, as a component in hydraulic brake fluids, in cleaning agents, detergents and disinfectants (EU 2000).

Metabolism

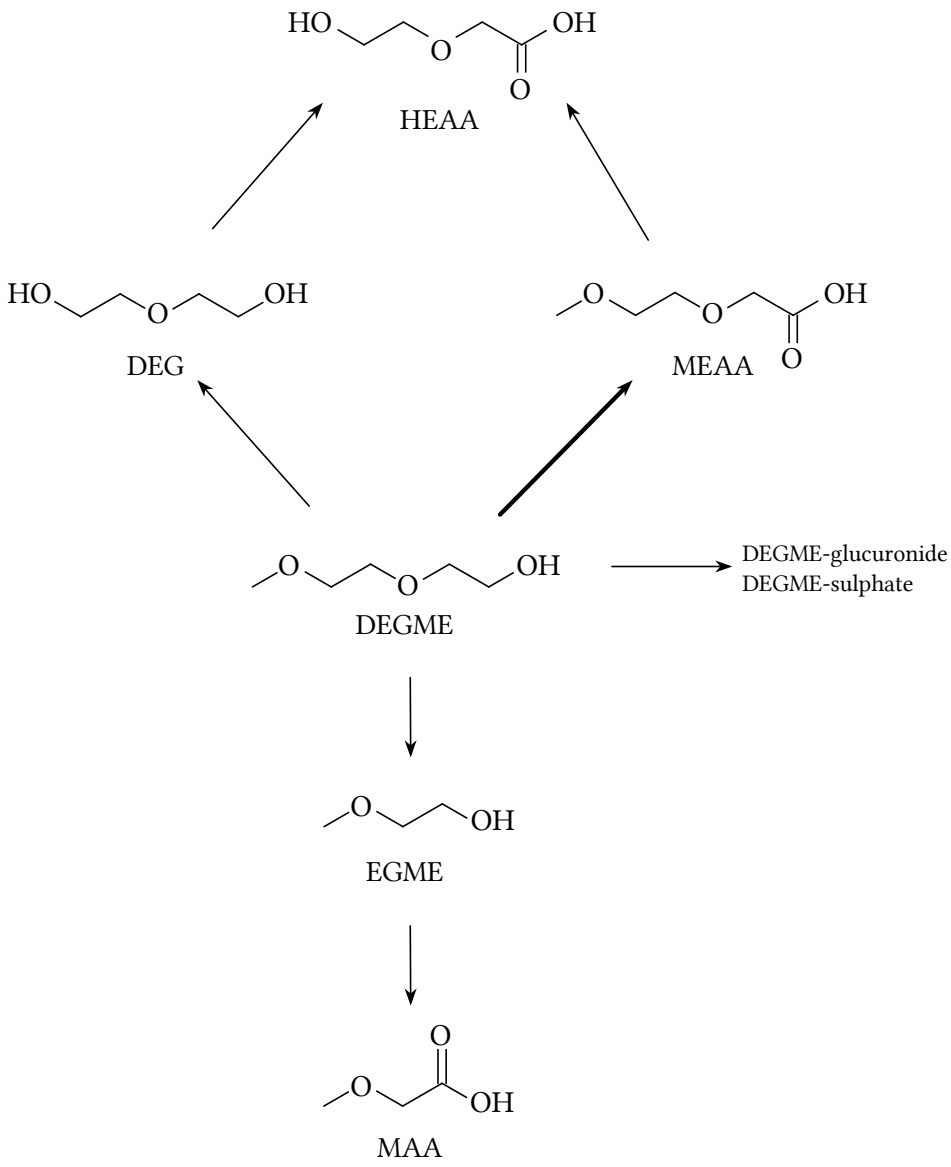
Regarding the internal exposure in the case of occupational exposure to diethylene glycol monomethyl ether, a study is available on workers exposed to jet fuel, where diethylene glycol monomethyl ether was used as an anti-icing agent. In this study 2-(2-methoxyethoxy)acetic acid was analysed as a metabolite of diethylene glycol monomethyl ether in urine (B'Hymer et al. 2012).

In the study by Kelsley et al. (2020), unmetabolised diethylene glycol monomethyl ether (3.4–4.9% of the administered dose) and the following metabolites were detected in the urine after gavage doses of 500, 1000 and 2000 mg diethylene glycol monomethyl ether/kg body weight in rats (proportion of the administered dose):

- 2-(2-Methoxyethoxy)acetic acid (87–95%)
- Methoxyacetic acid (0.8–1.4%)
- Diethylene glycol (1.6–2.4%)
- Diethylene glycol monomethyl ether glucuronide (0.7–1.0%)
- Diethylene glycol monomethyl ether sulfate (≈0.03%)
- 2-Hydroxyethoxyacetic acid (HEAA) (0.2–0.3%)
- two unknown metabolites (≈0.1%)

Unmetabolised diethylene glycol monomethyl ether and all metabolites except methoxyacetic acid were excreted in the urine with an estimated half-life of 3–4 hours after administration. Methoxyacetic acid showed a significantly longer elimination half-life, increasing with increasing dose from 14 to 36 hours (Kelsey et al. 2020).

The postulated metabolism of diethylene glycol monomethyl ether in rats is shown in Figure 1 (Kelsey et al. 2020).



DEG: diethylene glycol; DEGME: diethylene glycol monomethyl ether; EGME: ethylene glycol monomethyl ether (2-methoxyethanol); HEAA: 2-(2-hydroxyethoxy)acetic acid; MAA: 2-methoxyacetic acid; MEAA: 2-(2-methoxyethoxy)acetic acid

Fig. 1 Postulated metabolism of diethylene glycol monomethyl ether in rats after administration by gavage (Kelsey et al. 2020; reproduced by permission of Elsevier, http://www.elsevier.com)

General mode of action/toxicity

The general mode of action and toxicity are described in detail in the MAK documentation (Hartwig and MAK Commission 2024). In animal studies, the acute toxicity of diethylene glycol monomethyl ether was low. Regarding chronic toxicity, relative organ weight changes, haematotoxic and fertility-damaging effects are of importance.

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 tested method by the Commission's Working Group "Analyses in Biological Material" (Göen et al. 2006).

Furthermore, the working group has provided a tested method for the determination of propylene and diethylene glycol ethers in urine using capillary gas chromatography with flame ionisation detector, with which diethylene glycol monomethyl ether can also be analysed (Angerer et al. 2008).

Relationship between external and internal exposure

In a study with 22 floor lacquerers, the relationship between the concentration of 2-(2-alkoxyethoxy)ethanols (including diethylene glycol monomethyl ether) in the air and the 2-(2-alkoxyethoxy)acetic acids in urine was investigated. For diethylene glycol monomethyl ether in air in the range of 0.59–0.93 ml/m^3, a mean concentration of 2-(2-methoxyethoxy)acetic acid of 4.9 ± 4.3 mmol/mol creatinine was determined (Laitinen and Pulkkinen 2005). The concentration of the metabolite 2-methoxyacetic acid was not analysed.

Evaluation of a BAT value

As the toxic effect of diethylene glycol monomethyl ether is attributed to the metabolite 2-methoxyacetic acid (Hartwig and MAK Commission 2024), also 2-methoxyacetic acid and its metabolic precursor 2-methoxyethanol are considered for the derivation of the BAT value. Only one study on 2-(2-methoxyethoxy)acetic acid in urine after exposure to diethylene glycol monomethyl ether in a kerosene-based fuel is available for the metabolism in humans, so that the proportion of 2-methoxyethanol formed from diethylene glycol monomethyl ether in human metabolism is not known. In rats, diethylene glycol monomethyl ether is metabolised to 2-methoxyethanol and 2-methoxyacetic acid (0.8–1.4%) after oral administration (Kelsey et al. 2020).

The BAT value for 2-methoxyethanol of 15 mg methoxyacetic acid/g creatinine is derived from the NOAEC (no observed adverse effect concentration) for haematological effects in humans obtained from occupational health studies (translated in Käfferlein et al. 2016). The NOAEC for testicular toxicity of 2-methoxyethanol in humans is in a comparable order of magnitude (Hartwig and MAK Commission 2021).

Compliance with this BAT value for 2-methoxyethanol protects against toxic effects caused by exposure to diethylene glycol monomethyl ether.

Based on these findings, a

BAT value for diethylene glycol monomethyl ether of 15 mg methoxyacetic acid/g creatinine

is established.

For the metabolite methoxyacetic acid, an elimination half-life of 77 hours is given for humans (calculated from the determination of methoxyacetic acid in urine after inhalation exposure to 16 mg 2-methoxyethanol/m^3) (Groeseneken et al. 1989). Due to the long half-life of methoxyacetic acid, accumulation is to be expected (SCOEL 2006). Sampling should therefore be done at the end of the shift on the last day of the working week after at least 2 weeks of exposure.

The developmental toxicity of diethylene glycol monomethyl ether is mediated via methoxyacetic acid. According to available data and toxicokinetic calculations, damage to the embryo/foetus is not to be expected up to a urine concentration of 2.5 mg methoxyacetic acid/g creatinine. Therefore, Pregnancy Risk Group B applies for the BAT value and a urine concentration of 2.5 mg methoxyacetic acid/g creatinine is the prerequisite for Pregnancy Risk Group C (Michaelsen et al. 2024).

Interpretation

The BAT value refers to normally concentrated urine in which the creatinine content should be in the range of 0.3–3 g/l (translated in Bader et al. 2016). As a rule, for urine samples outside the above-mentioned limits, it is recommended to repeat the measurement in the normally hydrated test person.

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

B'Hymer C, Mathias P, Krieg E Jr, Cheever KL, Toennis CA, Clark JC, Kesner JS, Gibson RL, Butler MA (2012) (2-Methoxyethoxy)acetic acid: a urinary biomarker of exposure for jet fuel JP-8. Int Arch Occup Environ Health 85(4): 413–420. https://doi.org/10.1007/s00420-011-0687-7

EU (European Union) (2000) European Union Risk Assessment Report. 2-(2-Methoxy)ethanol. CAS No. 111-77-3. EINECS No. 203-906-6. Luxembourg: EU. https://echa.europa.eu/documents/10162/6d525882-1aae-407f-a17a-e182fd94a6da, accessed 03 Apr 2023

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. https://doi.org/10.1002/3527600418.bi62545e0010

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E (1989) Experimental human exposure to ethylene glycol monomethyl ether. Int Arch Occup Environ Health 61(4): 243–247. https://doi.org/10.1007/BF00381421

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

Hartwig A, MAK Commission (2024) Diethylenglykolmonomethylether. MAK-Begründung. MAK Collect Occup Health Saf 9(1): Doc003. https://doi.org/10.34865/mb11177d9_1or

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/https://doi.org/10.1002/3527600418.bb10986e1615

Kelsey JR, Cnubben NHP, Bogaards JJP, Braakman RBH, van Stee LLP, Smet K (2020) The urinary metabolic profile of diethylene glycol methyl ether and triethylene glycol methyl ether in Sprague-Dawley rats and the role of the metabolite methoxyacetic acid in their toxicity. Regul Toxicol Pharmacol 110: 104512. https://doi.org/10.1016/j.yrtph.2019.104512

Laitinen J, Pulkkinen J (2005) Biomonitoring of 2-(2-alkoxyethoxy)ethanols by analysing urinary 2-(2-alkoxyethoxy)acetic acids. Toxicol Lett 156(1): 117–126. https://doi.org/10.1016/j.toxlet.2003.09.022

Michaelsen S, Bartsch R, Brinkmann B, Schriever-Schwemmer G, Drexler H, Hartwig A, MAK Commission (2024) 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 of 2024. MAK Collect Occup Health Saf 9(1): Doc021. https://doi.org/10.34865/bb62545e9_1ad

SCOEL (Scientific Committee on Occupational Exposure Limits) (2006) Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-methoxyethanol and 2-methoxyethyl acetate. SCOEL/SUM/120. Brussels: European Commission. https://ec.europa.eu/social/BlobServlet?docId=3865&langId=en, accessed 13 Jul 2022