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2-Methoxyethanol and 2-methoxyethyl acetate – Addendum: re-evaluation of the BAT value

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

T. Göen[1]
H. Drexler[2,*]
A. Hartwig[3,*]
MAK Commission[4,*]

1 *Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine, Henkestraße 9–11, 91054 Erlangen, 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)*

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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 2-methoxyethanol [109-86-4] and 2-methoxyethyl acetate [110-49-6] to derive a biological tolerance value (BAT value) considering all toxicological end points. In 2008, the Commission derived a BAT value of 15 mg methoxyacetic acid/g creatinine for 2-methoxyethanol and 2-methoxyethyl acetate based on the haematotoxic effects in humans occupationally exposed to 2-methoxyethanol. In this article, new data on toxicity and toxicological mechanisms mainly regarding testicular toxicity are evaluated. The data are compliant with the former assessment that testicular toxicity is in the same order of magnitude as haematotoxicity. As a result, the BAT value of 15 mg methoxyacetic acid/g creatinine is confirmed. Sampling time is at the end of the shift on the last day of the working week after at least 2 weeks of exposure.

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BAT value (2008)	**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-Wert (2008) 2-Methoxyethanol	**1 ml/m³ ≙ 3.2 mg/m³**
MAK-Wert (2008) 2-Methoxyethyl acetate	**1 ml/m³ ≙ 4.9 mg/m³**
Absorption through the skin (1980)	H
Carcinogenicity	–

Re-evaluation

2-Methoxyethanol is a solvent for lacquers and paints and has also been used as a cleaning agent for the manufacture of circuit boards as well as for leather dyeing. It could be found in industrial varnish cleaners and cleaning agents for surfaces, and was employed for the manufacture of oven-drying industrial coatings. Due to its reproductive toxicity, in both industrial processes and consumer products, legal regulations have led the substance to be increasingly replaced by other solvents.

In 1983, the Commission derived maximum workplace concentrations (MAK values) of 5 ml 2-methoxyethanol/m³ (15 mg/m³) and 5 ml 2-methoxyethyl acetate/m³ (25 mg/m³) (translated in Henschler 1993); these values were reduced to 1 ml 2-methoxyethanol/m³ (3.2 mg/m³) and 1 ml 2-methoxyethyl acetate/m³ (4.9 mg/m³) in 2008 (Hartwig 2009). In 2008, BAT values of 15 mg methoxyacetic acid/g creatinine were also derived for 2-methoxyethanol and 2-methoxyethyl acetate (translated in Käfferlein et al. 2016).

New studies have been published since then which appear to necessitate a review.

Mode of action

Detailed information on the effects of 2-methoxyethanol can be found in Henschler (1993) and Hartwig (2009). 2-Methoxyethanol exhibits low acute toxicity and, after repeated exposure, primarily damages the haematopoietic and lymphatic organs, the germinal epithelium of the testes, embryonic or foetal tissue, and, to a lesser extent, the kidneys, liver, and nervous system. The substance furthermore is teratogenic. In rabbits, undiluted 2-methoxyethanol led to neither skin nor eye irritation. In vitro, high concentrations of 2-methoxyethanol and 2-methoxyethyl acetate induce clastogenic effects. A maximisation test in guinea pigs did not indicate a skin sensitising effect.

Results from experiments on animals

A number of animal studies have been published since the last evaluation.

To acquire a mechanistical understanding of the toxicity induced by 2-methoxyethanol, Takei et al. (2010) performed a metabolomic analysis in **rats**. Oral doses of 30 and 100 mg 2-methoxyethanol/kg body weight (bw) per day were administered to male Fischer 344 rats. Serum, urine, liver, and testes were taken for analysis on days 1, 4, and 14. Testicular damage was observed only on day 14 in the group given 100 mg/kg bw per day. About 1900 intermediary products of physiological metabolic pathways were detected in the four matrices by mass spectrometry. The most prominent metabolic disruptions by 2-methoxyethanol concerned choline oxidation, amino acid degradation, and fatty-acid β-oxidation. All impaired metabolic steps were catalysed by the enzymes of the primary flavoprotein-dehydrogenase family.

Sakurai et al. (2015) exposed three sexually mature male **cynomolgus monkeys** to an oral dose of 300 mg 2-methoxyethanol/kg bw on four consecutive days; three other monkeys were not exposed and served as controls. Circulatory and testicular microRNA profiles were examined. The dose of 300 mg/kg bw of 2-methoxyethanol induced testicular toxicity in all monkeys.

In order to determine the effects of 2-methoxyethanol on the female reproductive system as well as the pubertal development of juvenile **rats**, Taketa et al. (2017) exposed female Sprague Dawley rats orally to 0, 50, 100, or 300 mg 2-methoxyethanol/kg bw from postnatal day 21 to day 45. This 2-methoxyethanol treatment led to a prolonged oestrus cycle which was characterised by persistent dioestrus at 50 mg/kg bw without any effects on body weight, the timing of vaginal opening, or the histology of the reproductive organs. A dose of 100 mg 2-methoxyethanol/kg bw induced a reduction in body weight gain, a delay in vaginal opening, and an irregular oestrus cycle with an absence of corpora lutea and hypertrophy of the uterine epithelium, which indicates an impairment of the ovulatory process related to hormonal effects. At a dose of 300 mg 2-methoxyethanol/kg bw, there was a statistically significant delay in the onset of puberty due to a strong retardation in growth.

Matsuyama et al. (2018) administered single oral doses of 200, 600, or 2000 mg 2-methoxyethanol/kg bw to male F344/DuCrlCrlj rats in order to evaluate changes in the transcription of genes, including spermatocyte-specific genes in the testes of **rats**, caused by 2-methoxyethanol. At 600 mg/kg bw and above, 2-methoxyethanol caused dose-dependent testicular toxicity, which was characterised by degeneration and necrosis of the spermatocytes in stage VII-XIV of the testicular tubuli. Overall, 2-methoxyethanol caused spermatocyte toxicity which correlated with a reduced expression of spermatocyte-specific genes. Furthermore, oxidative stress, the activation of protein kinases, and histone acetylation appear to be involved in the testicular toxicity induced by 2-methoxyethanol.

Adeyemo-Salami and Farombi (2018) studied the effects of 2-methoxyethanol on the antioxidative system of the reproductive organs with 50 male Wistar **rats** (in five groups). Group I received distilled water; Groups II–V received oral doses of 100, 200, 300, or 400 mg 2-methoxyethanol/kg bw over a period of 14 days. On the fifteenth day, the animals were killed and the reproductive organs were examined. Both weekly weight gain as a percentage and the relative weight of the testes decreased significantly among the treatment groups ($p < 0.05$). Analysis of spermatozoa showed decreases in the treatment groups. Various antioxidative parameters in the testes and epididymides, such as superoxide dismutase and glutathione *S*-transferase, were affected. The histopathological results confirm the biochemical findings.

Somade et al. (2020) investigated the time-dependent effects of 2-methoxyethanol on the testicular cells of male Wistar **rats**. The animals received 50 mg 2-methoxyethanol/kg bw orally on 7, 14, or 21 days. A variety of biomarkers, such as those for oxidative stress, apoptosis, and inflammatory markers, were significantly altered in some cases. After 7, 14, and 21 days, a severe loss of seminiferous tubules was observed in the testes. The testicular epithelium exhibited very few spermatocytes, spermatids, spermatogonia, spermatozoa, and Sertoli cells, while the interstitial tissue was eroded and displayed sparse, abnormal Leydig cells.

Shing et al. (2021) investigated whether circulatory microRNA might serve as an early screening marker for testicular toxicity and used 2-methoxyethanol as a testicular-damaging agent. Two castrated and two non-castrated beagle **dogs** were administered an oral dose of 50 mg 2-methoxyethanol/kg bw for 14 to 28 days. As an excessively high exposure to 2-methoxyethanol was selected, already causing light to moderate degeneration of the testes and epididymides, this study is not suitable to identify early parameters.

Re-evaluation of the BAT value

Since the last evaluation of 2-methoxyethanol, no new epidemiological studies have been published which would be relevant for the re-evaluation of the BAT value. In the animal studies published since the last evaluation, animal models exclusively used dosages of 2-methoxyethanol which clearly exceeded the NOAEL (no-observed-adverse-effect levels) identified to date. As such, these new data did not provide sufficient evidence to question the effect threshold previously

established or the finding that the haematotoxic effects, as observed in humans, were of a similar magnitude as testicular toxicity, and that these represented the most sensitive toxic effects.

Therefore, the

BAT value for 2-methoxyethanol of 15 mg methoxyacetic acid/g creatinine

is confirmed. This BAT value is also valid for 2-methoxyethyl acetate.

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 2-methoxyethanol and 2-methoxyethyl acetate 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 and analytical conditions

The BAT value refers to normally concentrated urine in which the creatinine content should be in the range of 0.3 to 3 g/l (translated in Bader et al. 2016). For urine samples outside of the aforementioned limits, it is generally recommended to repeat the measurement when the test person is normally hydrated.

2-Methoxyethanol is absorbed through the skin extremely well, such that dermal exposure in the workplace may, under certain conditions, be an important route of uptake, if not the most important. However, because dermal absorption of this substance proceeds very rapidly and because, at the same time, renal excretion is a generally very slow process, a higher proportion of dermal exposure does not influence the measurement strategy or the interpretation of the findings.

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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