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Methoxyacetic acid – Evaluation of a BAT value

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

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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 methoxyacetic acid [625-45-6] to derive a biological tolerance value (BAT value) considering all toxicological end points. There are no toxicological data from humans occupationally exposed to methoxyacetic acid. For methoxyethanol, a substance which is efficiently metabolised to the toxic methoxyacetic acid, many human studies provide sufficient toxicological data as well as toxicokinetic information on the metabolite. A BAT value of 15 mg methoxyacetic acid/g creatinine was derived for 2-methoxyethanol based on the haematotoxic effects in occupationally exposed individuals in 2008. The BAT value was confirmed in 2023. As a result, the BAT value of 15 mg methoxyacetic acid/g creatinine was likewise derived for exposure to methoxyacetic acid. 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 (2022)	**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 (2008)	**1 ml/m³ ≙ 3.7 mg/m³**
Absorption through the skin (2008)	H
Carcinogenicity	–
Synonyms	2-Methoxyacetic acid Methoxyglycolic acid Methoxyethanoic acid

Methoxyacetic acid was used as a disinfectant and as a cleaning agent for the decalcification of surfaces. Due to its toxic effect on reproduction, methoxyacetic acid was included in the ECHA's list of SVHC substances (substances of very high concern) (ECHA 2012)

In 1998, the Commission derived a maximum workplace concentration (MAK value) of 5 ml methoxyacetic acid/m³ (19 mg/m³) for methoxyacetic acid in analogy to 2-methoxyethanol (Greim 2000); this value was reduced, again in analogy to 2-methoxyethanol, to 1 ml methoxyacetic acid/m³ (3.7 mg/m³) in 2008 (Hartwig 2009 b). While the acute irritant effects on airways and mucous membranes was seen as the most sensitive endpoint for the MAK value of 5 ml methoxyacetic acid/m³ (19 mg/m³) in the evaluation from 1998, systemic effects following chronic exposure are relevant for the current MAK value of 1 ml methoxyacetic acid/m³ (3.7 mg/m³). Initially, a biological tolerance value (BAT value) for methoxyacetic acid was not derived.

Mode of action and toxicokinetics

Methoxyacetic acid is active both locally and systemically. In high concentrations, the substance has a corrosive effect on the skin. Inhalation studies in rats and mice proved methoxyacetic acid to be irritating to mucous membranes as well as degenerative to the olfactory epithelium. Systemically, the haematotoxicity and reproductive toxicity of the substance are most critical. The embryotoxic effects of methoxyacetic acid are similarly important (Hartwig 2009 a; Hartwig and MAK Commission 2018).

The MAK value for methoxyacetic acid was established in 2008 in analogy to 2-methoxyethanol, which was better studied, because methoxyacetic acid is the main metabolite of 2-methoxyethanol and is responsible for its haematotoxicity and reproductive toxicity.

Methoxyacetic acid is rapidly absorbed following oral application. For monkeys, the mean half-life in plasma was 24 hours. In mice 24 hours after oral administration, 2.2% of the substance was exhaled as CO_2 and 70% was excreted with the urine; of this amount, 35% was excreted unchanged and 22% as the glycine conjugate of methoxyacetic acid (Greim 1998).

The only data on the toxicokinetics of methoxyacetic acid in humans are available for exposure to 2-methoxyethanol or 2-methoxyethyl acetate. At 77 hours, the elimination half-life of methoxyacetic acid in humans is considerably longer than in (pregnant) rats (12 hours) and monkeys (19 hours) (Hartwig 2009 a).

Experiences with occupationally exposed individuals further show that methoxyacetic acid is excreted in human urine only unchanged and in its non-conjugated form (translated in Käfferlein et al. 2016).

Analytical methods

A method tested by the Commission using the GC-MS technique is available for the determination of methoxyacetic acid and other alkoxycarboxylic acids in urine (Göen et al. 2006).

Background exposure

A study by Fromme et al. (2013) is available on the excretion of methoxyacetic acid in the urine of individuals in the German general population without occupational contact with methoxyacetic acid or methoxyacetic acid-forming glycol ethers. Methoxyacetic acid was detected in every urine sample from 44 subjects from southern Germany (31 women and 13 men) at a limit of detection (LOD) of 0.01 mg/l. A median of 0.11 mg/l or 15 mg/g creatinine, respectively, was ascertained as well as a 95th percentile of 0.30 mg/l or 0.38 mg/g creatinine, respectively. The exposure levels determined in this study are very consistent with data from a larger population study from France (Garlantézec et al. 2012; Labat et al. 2008: 451 pregnant women; 28.8% < LOD (0.05 mg/l); geometric mean ≥ LOD: 0.11 mg/l, 75th percentile: 0.06 mg/l; maximum value: 2.97 mg/l).

Evaluation of a BAT value

There are no published studies on workplace exposure to methoxyacetic acid, specifically no epidemiological studies, which could be used for the direct derivation of a BAT value. Since methoxyacetic acid is the main metabolite of 2-methoxyethanol and is also responsible for the haematotoxicity and reproductive toxicity of this substance, and because 2-methoxyethanol is better studied in the fields of occupational medicine and epidemiology, the derivation of the BAT value for methoxyacetic acid is based on the data for 2-methoxyethanol.

In 2008, a BAT value of 15 mg methoxyacetic acid/g creatinine was derived for 2-methoxyethanol based on an occupational-medical study in which haematotoxic effects in workers were directly juxtaposed against concentrations of methoxyacetic acid in the urine samples from the exposed individuals (Käfferlein et al. 2016). This BAT value was confirmed in 2023 after evaluating the currently available data, with a particular focus on reproductive toxicity (Göen et al. 2024). As the BAT value was derived directly from the correlation between systemic effects and internal exposure to methoxyacetic acid, this value can be adopted for the assessment of occupational exposure to methoxyacetic acid.

Therefore, a

BAT value for methoxyacetic acid 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.

Methoxyacetic acid causes developmental toxicity. 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 to 3 g/l (translated in Bader et al. 2016). For urine samples outside the abovementioned limits, it is generally recommended to repeat the measurement on a 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.

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