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Methoxyacetic acid

MAK Value Documentation

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DOI: 10.1002/3527600418.mb62545e6018

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of 1 ml/m³ for methoxyacetic acid [625-45-6] considering the endpoints local and systemic toxicity as well as developmental toxicity. Methoxyacetic acid acts locally as well as systemically. It is the metabolite responsible for the haematotoxicity and reproductive toxicity of the better investigated methoxyethanol. Hence, the MAK value of 1 ml methoxyethanol/m³ was also assigned to methoxyacetic acid in 2008. A 28-day study with rats shows a NOAEC for systemic and local effects of 15 ml/m³. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. According to this approach, a concentration of 0.9 ml/m³ for the workplace air can be calculated from this study. Therefore, the MAK value of 1 ml/m³ is confirmed. Systemic as well as local effects are critical and the assignment to Peak Limitation Category II for systemic effects is retained. However, to avoid sensory irritation, the former excursion factor of 8 seems too high and is reduced to 2 in analogy to the excursion factors for formic acid and acetic acid. The assignment to Pregnancy Risk Group B, substances for which damage to the embryo or foetus cannot be excluded even when the MAK value is observed, is confirmed.

Completed: March 23, 2015

Keywords

methoxyacetic acid; MAA; (sub)acute toxicity; (sub)chronic toxicity; irritation; peak limitation; prenatal toxicity; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Methoxyacetic acid

[625-45-6]

Supplement 2016

MAK value (2008)	**1 ml/m³ (ppm) ≙ 3.7 mg/m³**
Peak limitation (2015)	**Category II, excursion factor 2**
Absorption through the skin (2008)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1998)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value (2008) for methylene glycol monomethyl ether and methylene glycol monomethyl ether acetate	**15 mg methoxyacetic acid/g creatinine in urine**
Vapour pressure at 20 °C	1–1.8 hPa (ECHA 2013)
log K_{OW}[1)]	–0.68 (calculated; ECHA 2013)
pKa value	3.57 (O'Flaherty et al. 1995)
pH	1.6 at 100 g/l (ECHA 2013)
1 ml/m³ (ppm) ≙ 3.7 mg/m³	**1 mg/m³ ≙ 0.27 ml/m³ (ppm)**

Methoxyacetic acid has both local and systemic effects. No new studies have become available since the supplement from 2009 (supplement "Methoxyessigsäure" 2009, available in German only). In 2008, the MAK value was established in analogy to the better investigated ethylene glycol monomethyl ether since methoxyacetic acid is the metabolite of ethylene glycol monomethyl ether that is responsible for its haematotoxicity and reproductive toxicity. The MAK value for ethylene glycol monomethyl ether was established on the basis of the BAT value. In the supplement from 2009 (supplement "Methoxyessigsäure" 2009, available in German only) it was

1) Octanol/water partition coefficient.

stated that at a concentration of 1 ml/m³ irritation is not the main effect of methoxyacetic acid.

For the derivation of MAK values for substances with effects on the upper airways and eyes, the Commission has since 2014 been using a procedure based on physiological and empirical aspects (Brüning et al. 2014), in which also the criteria for categorization as a sensory irritant are described. The MAK value has been re-evaluated on the basis of this procedure.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

In a 28-day inhalation study (6 hours/day, 5 days/week, nose-only exposure) with methoxyacetic acid concentrations of 20, 60 and 160 mg/m³ in vapour form (6.1, 15.8, 42 ml/m³) the NOAEC (no observed adverse effect concentration) was 60 mg/m³ for systemic effects and impairment of fertility in rats. Histological examination of the nose revealed the following findings: hyperplasia of the transitional epithelium, goblet cell hyperplasia and inflammatory cell infiltrates in the mucosa und submucosa increased in severity and incidence in a concentration-dependent manner at 60 mg/m³ and above. Due to the small number of animals (5 animals per sex and concentration group), it is, however, not possible to make a valid statement regarding the statistical significance of the results (BG Chemie 1994). The NOAEC is presumably in the range of 60 mg/m³ (15.8 ml/m³); however, in a few animals the incidence of some findings at this concentration was higher than the control incidences.

The acidity of methoxyacetic acid is similar to that of formic acid (pKa 3.7). The NOAEC for formic acid was found to be 32 ml/m³ after 2 weeks of exposure in rats and 16 ml/m³ after 13 weeks (degeneration of the olfactory epithelium, in only one rat in each case at 32 ml/m³ and 64 ml/m³ in the 13-week study); in mice the NOAEC was given as 32 ml/m³ after both 2 and 13 weeks (documentation "Ameisensäure" 1997, available in German only). There is therefore no marked decrease in the NOAEC over time. A similar result is expected for methoxyacetic acid.

Local effects on skin and mucous membranes

Methoxyacetic acid is corrosive to the skin. For this reason, eye irritation was not tested.

Manifesto (MAK value/classification)

The critical effects are haematotoxicity, reproductive toxicity and irritation.

MAK value.
In 2008, the MAK value of 1 ml/m³ was established in analogy to the better investigated ethylene glycol monomethyl ether since methoxyacetic acid is the metabolite of ethylene glycol monomethyl ether that is responsible for its haematotoxicity and reproductive toxicity. The local effects on the nasal epithelium in rats have been re-assessed. In accordance with the procedure described by Brüning et al. (2014), and taking into consideration both the assumed increase in effects with increasing exposure duration as data for long-term exposure are not available (1:6) and the extrapolation of nasal effects to humans (1:3), a concentration of 0.9 ml/m³ is calculated from the NOAEC of 15.8 ml/m³. This concentration is likewise obtained when the safer value of 6.1 ml/m³ is taken as the NOAEC and a similar ratio of the NOAEC from the 2-week study with formic acid (32 ml/m³) to the MAK value (5 ml/m³) is taken as a basis. In both cases this means that the NAEC for local effects is in the same order of magnitude as that for the systemic effects derived from the BAT value for ethylene glycol monomethyl ether, and that the MAK value of 1 ml/m³ can be retained.

Peak limitation.
As methoxyacetic acid, in addition to its systemic effect (which has led to classification in Peak Limitation Category II), also causes local irritation in a similar concentration range, the previous excursion factor of 8 appears to be too high. An excursion factor of 2 has now been established in analogy to and using the data available for formic acid and acetic acid.

Prenatal toxicity.
There are no new studies available for the prenatal toxicity of methoxyacetic acid.

Since 1998, methoxyacetic acid, as the main metabolite of ethylene glycol monomethyl ether, has been classified in Pregnancy Risk Group B because it is responsible for the latter's developmental toxicity (documentation "Methoxyessigsäure" 1998, available in German only).

In 1985, ethylene glycol monomethyl ether was classified in Pregnancy Risk Group B due to its teratogenicity. Even after the lowering of the MAK value from 5 to 1 ml/m³, the difference to the NOAEC for developmental toxicity of 3 ml/m³, to that for foetotoxicity of 10 ml/m³ and to that for teratogenicity of 50 ml/m³—especially in view of its ready absorption through the skin—is relatively small, so that classification of the substance in Pregnancy Risk Group B was retained in 2009 (supplement "2-Methoxyethanol" 2009, available in German only).

As the MAK value of 1 ml/m³ for methoxyacetic acid has been confirmed, classification of the substance in Pregnancy Risk Group B has been retained.

Sensitization.
There are still no clinical findings or data from animal experiments available for sensitizing effects of methoxyacetic acid. The substance is therefore not designated with "Sa" or "Sh" (for substances which cause sensitization of the airways and skin).

References

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completed 23.03.2015