# Addendum to Methyl bromide / Bromo methane

## BAT Value Documentation

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### Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the BLW ("Biologischer Leitwert") for methyl bromide, using bromide in serum/plasma to characterise the internal exposure. The critical effect of methyl bromide is a high acute and chronic neurotoxicity. It can pass through the skin so that biological monitoring is highly recommended.
On the basis of results of a human study the occurrence of abnormal findings in the EEG is comparable for unexposed persons and persons with exposure to methyl bromide in concentrations below 12 mg bromide/l plasma. Thus the BLW of 12 mg bromide/l plasma or serum was confirmed. The sampling time for long-term exposure is at the end of exposure/shift after several previous shifts.
The evaluation of an EKA for methyl bromide in the air and S-methylcysteine-albumin adducts in blood is not possible as there is insufficient data available.

### Keywords

methyl bromide; bromomethane; monobromomethane; occupational exposure; biological tolerance value; BAT value; BLW; EKA; toxicity

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# Addendum to Methyl bromide

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|---|---|
| **BLW (2002, 2014)** | **12 mg bromide/l plasma or serum** |
| | Sampling time: for long-term exposures: at the end of the shift after several shifts |
| **EKA (1998, 2014)** | **not established** |
| | Sampling time: not fixed |
| **MAK value (2010)** | **1 ml/m³ ≙ 3.9 mg/m³** |
| Absorption through the skin | – |
| Carcinogenicity (1992) | Carcinogen category 3 B |

## 1 Re-evaluation

Methyl bromide was evaluated in 1998. EKA (exposure equivalents for carcinogenic substances) for the parameter S-methylcysteine-albumin could not be established.

In 2010 a MAK value of 1 ml/m³ (1 ppm) and a peak limitation category I with an excursion factor 2 were established for methyl bromide. Its classification in carcinogen category 3 B from 1992 was confirmed. Methyl bromide was classified in pregnancy risk group D (2010). Designation with an "H" has been withdrawn (Hartwig 2011). Therefore the BLW ("Biologischer Leitwert") of 12 mg bromide/l plasma or serum, which was derived on the basis of neurotoxic effects, was reviewed.

According to the Montreal Protocol on Substances that Deplete the Ozone Layer methyl bromide should no longer be in use in developed countries since 2005; for developing countries there was a transitional phase-out period until 2015. As there is a lack of alternative and similarly cost-effective fumigants, numerous exemptions, especially in agriculture (Norman 2005) and in the transport industry (Budnik et al. 2012), have been applied for.

The data for the epidemiology, genotoxicity, reproductive toxicity and toxicokinetics of methyl bromide can be found in the documentation of the MAK value (Hartwig 2011; Henschler 1992, translated). The data on the metabolism and kinetics, on the methods used, on background exposure and interpretation of results are presented in the documentation of the BLW (see BAT Documentation 2002, translated). In the meantime new data on the chronic toxicity, external exposure and selection of indicators have been published.

## 1.1 Chronic toxicity

For the chronic effects of methyl bromide the reader is referred to the MAK and BAT Documentations (see BAT Documentation 2002, translated; Hartwig 2011). In addition, case reports of erectile dysfunctions and potency disorders have been described (Magnavita 2009; Park et al. 2005).

## 1.2 External exposure

In 2010 the designation of methyl bromide with an "H" has been withdrawn (Hartwig 2011). Based on the results of a case study (Zwaveling et al. 1987) and of model calculations no toxicologically relevant contribution of dermal absorption is to be expected when the MAK value is observed. Peak exposures and intoxication due to improper handling of the fumigant, often together with a lack of or inadequate protective clothing occur frequently. Increasingly there are also unexpected exposures in the transport sector, for example when handling or transshipping transport containers (Breeman 2009; Budnik et al. 2012).

## 1.3 Selection of indicators

Compared with other parameters the determination of the bromide concentration in blood and urine as indicator of exposure to methyl bromide has proved useful and reliable in clinical and occupational health practice. The parameter bromide is, however, not specific for an exposure to methyl bromide, a fact which has to be taken into account in the case of co-exposure to other substances.

Table 1 and Table 2 give an overview of the bromide concentrations measured in cases of acute intoxications and of those determined in occupational health studies to detect chronic exposure.

The determination of reaction products (adducts) with macromolecules in blood, especially serum albumin and haemoglobin, in principle appears to be a suitable biomonitoring parameter. The derivation of a threshold limit value for these parameters, however, is not possible, as there are no reliable data available at present.

## 1.4 Evaluation

Since the evaluation of the BLW in 2002 three more recent occupational health studies have become available (Akca et al. 2009; Magnavita 2009; Yamano et al. 2011). Their results are presented in Table 1 and Table 2.

The parameter bromide in urine in general proved to be practicable for monitoring exposed collectives. However, no new insights are available for the derivation of a threshold limit value. The BLW is therefore still based on the investigations by Verberk et al. (1979) (see BAT Documentation 2002, translated). This study describes the abnormalities in the EEG of workers exposed to methyl bromide in relation to their blood bromide concentrations. Abnormalities in the EEG were found in 60% of the workers with bromide levels of more than 12 mg/l.

**Table 1** Bromide concentration in cases of acute intoxications and in occupational health studies to detect chronic exposure

| n | Bromide concentration (matrix) | References |
|---|---|---|
| | **Acute intoxications** | |
| 3 | 67.8–91.5 mg/l (plasma) | Yamano et al. 2001 |
| 1 | 43.7 mg/l (serum) | Ichikawa et al. 2001 |
| 1 | 202 mg/l (plasma) | Hoizey et al. 2002 |
| 1 | 11.2 mg/l (serum)<br>37.1 mg/l (urine) | Park et al. 2005 |
| 3 | 87.4–164.9 mg/l (serum)<br>75.3–122.4 mg/g creatinine (urine) | Yamano and Nakadate 2006 |
| 2 | 39.1 mg/l (serum, one person affected) | Kang et al. 2006 |
| 1 | 81.8 mg/l (serum) | Suwanlaong and Phanthumchinda 2008 |
| 9 | 37–220 mg/l (blood) | Hewitt and Gandy 2009 |
| 10 | 11.7–39.6 mg/l (serum)<br>7.6–94.6 mg/l (urine) | Kim and Kang 2010 |
| 2 | 15–44 mg/l (serum) | CDC 2011 |
| | **Occupational health studies** | |
| 6 | 0.8–6.0 mg/l (serum) | Magnavita 2009 |
| 20 | 3.4–20.6 mg/l (serum) | Akca et al. 2009 |
| 124 | 2.5–51.8 mg/g creatinine [synthesis]<br>3.1–34.8 mg/g creatinine [filling]<br>1.7–14.6 mg/g creatinine [other production jobs, temps] | Yamano et al. 2011 |

**Table 2** Analyses in air, bromide concentrations and observed clinical symptoms after incidents of elevated exposure (Yamano et al. 2011)

| n | Concentration in air [ml/m³] | Bromide concentration (matrix) | Clinical symptoms |
|---|---|---|---|
| 3 | 39.8 | 36.2–52.3 mg/l (serum)<br>34.2–68.7 mg/g creatinine (urine) | none |
| 4 | 25.5 | 20.7–68.5 mg/l (serum)<br>22.6–83.4 mg/g creatinine (urine) | none |
| no data | 14 | 3.0–22.3 mg/g creatinine (urine) | none |
| 1 | no data | 56.2 mg/g creatinine (urine) | burns on the hands[*1] |
| 1 | no data | 11.5 mg/g creatinine (urine) | burns on the head[*1] |
| 1 | no data | 39.5 mg/g creatinine (urine) | dizziness[*2] |

[*1] after contact with liquid methyl bromide

[*2] after inhalation of methyl bromide

Below a bromide level of 12 mg/l the frequency of abnormal EEG findings (17%) is hardly any different to that in healthy control persons not exposed to methyl bromide (10%). The authors of the study therefore suggest 12 mg bromide/l plasma or serum as a cut-off value for the occurrence of abnormal findings in the EEG.

For this reason the **BLW** of

**12 mg bromide/l plasma or serum**

is confirmed.

Sampling for long-term exposure should be carried out for long-term exposure at the end of the shift after several previous shifts.

The evaluation of an EKA for methyl bromide in the air and S-methyl-cysteine-albumin adducts in blood is not possible as there is insufficient data available.

## 2 References

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