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## Addendum to 2-Butoxyethanol (ethylene glycol monobutyl ether)

### Assessment Values in Biological Material – Translation of the German version from 2016

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**Keywords:** 2-butoxyethanol; ethylene glycol monobutyl ether; butoxy acetic acid; biological tolerance value; BAT value

**Citation Note:** Göen T, Rettenmeier A, Drexler H, Hartwig A, MAK Commission. Addendum to 2-Butoxyethanol (ethylene glycol monobutyl ether). Assessment Values in Biological Material – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2018 Oct;3(4):2041-2047]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. [https://doi.org/10.34865/bb11176e2218\\_w](https://doi.org/10.34865/bb11176e2218_w)

**Republished (online):** 06 Mar 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; <https://doi.org/10.1002/3527600418.bb11176e2218>

**Addendum completed:** 20 Feb 2015

**Published (online):** 19 Oct 2018

*The commission established rules and measures to avoid conflicts of interest.*



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## BAT Value Documentation

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DOI: 10.1002/3527600418.bb11176e2218

### Abstract

In 2015 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the biological tolerance value at the work place (BAT value) for 2-butoxyethanol (ethylene glycol monobutyl ether) [CAS No. 111-76-2], considering butoxyacetic acid in urine to characterise the internal exposure. The main systemic adverse effects of 2-butoxyethanol are on the haematopoietic system (haemolytic effects), followed by possible teratogenic and testicular effects. 2-Butoxyethanol was classified in category 4 for carcinogenic substances, which enables the evaluation of a health based exposure limit. It can easily pass through the skin, so biological monitoring is necessary for a valid individual risk assessment. A considerable part of the absorbed 2-butoxyethanol is excreted in form of the glutamine conjugate of butoxyacetic acid, i.e. N-butoxyacetyl glutamine. The relative amount of this conjugate in the total excretion of butoxyacetic acid varied considerably intra- and inter-individually depending on the exposure levels and possibly on enzyme polymorphisms. On average half of the total butoxyacetic acid is excreted in the form of the glutamine conjugate (factor 2). Various studies indicate that at high exposure levels the capacity of the conjugate reaction is exceeded and lower conjugated amounts appear. Due to the high variability of conjugated amounts of the butoxyacetic acid and the limitation of conjugated amounts at high exposure levels the previous BAT value for free 2-butoxyacetic acid is converted with a factor of 1.5 to the total amounts of 2-butoxyacetic acid. Additionally, the impact of diuresis is considered by the relation to the creatinine concentration. Therefore, a BAT value for the total butoxyacetic acid excretion of 150 mg butoxyacetic acid (after hydrolysis)/g creatinine was established. Sampling should be performed at the end of exposure and shift, respectively, after several previous shifts. This BAT value applies also for combined exposure to 2-butoxyethanol and 2-butoxyethylacetate.

### Keywords

2-butoxyethanol; ethylene glycol monobutyl ether; occupational exposure; biological tolerance value; BAT value; toxicity

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## BAT (2015)

**150 mg butoxyacetic acid (after hydrolysis)/g creatinine**

Sampling time: end of exposure or end of shift; for long-term exposures: after several shifts

## MAK value (2006)

**10 ml/m<sup>3</sup> (ppm)  $\triangleq$  49 mg/m<sup>3\*</sup>**

Absorption through the skin (1980)

H

Carcinogenicity (2006)

Carcinogen Category 4

\* MAK value for the sum of the air concentrations of ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate

## 10 Re-evaluation of the BAT value (Biological Tolerance Value)

In 2008, in addition to the existing BAT value of 100 mg free butoxyacetic acid/l urine, a further BAT value of 200 mg butoxyacetic acid (after hydrolysis)/l urine was established. As the MAK value was derived on the basis of the irritant effects of the substance (Greim 2007 a, b, translated), the BAT values were derived based on systemic effects (haemolysis). Since then, further studies on the toxicokinetics of these substances have been published which make a re-evaluation of the BAT value for ethylene glycol monobutyl ether (EGBE) and ethylene glycol monobutyl ether acetate (EGBEA) necessary.

### 10.1 Metabolism and toxicokinetics

As shown in the BAT Documentations of 1996 and 2009, EGBE and EGBEA are very readily absorbed both via the airways and through the skin (see BAT Documentations 1996, translated; 2009, translated).

Most of the EGBE absorbed by the human organism is metabolically oxidized to butoxyacetic acid (BAA), which is excreted with the urine either in free form or as glutamine conjugate (N-butoxyacetyl glutamine) and, in small quantities, also as glycine conjugate (see BAT Documentations 1996, translated; 2009, translated;

Wodarz and Rettenmeier 1991). The data given for the proportion of BAA excreted in conjugated form in relation to total excretion vary between 0% and 100% (Jones and Cocker 2003; Kezic et al. 2004). Rettenmeier et al. (1993) analyzed the excretion of BAA in the urine of 6 workers processing lacquers containing EGMBE. The fraction of conjugates was 16% to 64% with total BAA excretion ranging from 33 to 925 mg/l. In the worker with the by far highest exposure the lowest rate of conjugate was found (16% vs 48%–64%).

Doerfler et al. (1996) investigated the renal BAA excretion of 25 persons exposed to EGBE during the manufacture of lacquers and paints. The total excretion of BAA was in the range of 8 to 205 mg/g creatinine and the fraction of conjugates in these samples ranged between 5% and 94%. Regression analysis revealed a significant inverse relationship between total excretion of BAA and the fraction of conjugates, i.e. the higher the total amount of BAA, the lower is the fraction of conjugated BAA. This suggests that the fraction of conjugates is dependent on the exposure level.

Corley et al. (1997) investigated the toxicokinetics of glycol ether in volunteers of whom one arm each was exposed in a gas atmosphere to  $^{13}\text{C}$ -labelled EGMBE at a concentration of 50 ml/m<sup>3</sup> for 2 hours. During the first 12 hours the fraction of conjugates in urine was between 54.4% and 74.1% with a total excretion of BAA in the range from 2.55 to 3.60 mg/g creatinine.

Jones and Cocker (2003) examined the urinary BAA excretion of 48 workers in the screen printing industry. Here too, there was an extremely wide variation in the conjugate fraction (0%–100%) with total excretions of BAA up to maximum 200 mg/g creatinine (see Jones and Cocker 2003, Figure 3). However, the data of Jones and Cocker did not show a clear relationship between the rate of conjugate formation and the total BAA excretion.

Kezic et al. (2004) analyzed the BAA excretion of volunteers exposed either by inhalation to 19 ml EGBE/m<sup>3</sup> for 30 minutes or dermally on an area of 40 cm<sup>2</sup> to an aqueous solution of 50% EGBE for 4 hours. They investigated both the course of total BAA excretion and that of the conjugate proportion up to 48 hours after the exposure. Directly after the exposure the total excretion of BAA was  $15.1 \pm 4.9$  mg/g creatinine (inhalation experiment) and  $300 \pm 70$  mg/g creatinine (dermal exposure), which then declined with half-lives of 3.4 and 5.1 hours, respectively. In both experiments the proportion of conjugate in the total excretion of BAA increased steadily after the end of exposure. Immediately after the dermal exposure the conjugate fraction was  $45\% \pm 30\%$  and increased up to  $92\% \pm 2\%$ . In the inhalation experiment, the conjugate fraction showed a similar course.

Šperlingová et al. (2010) reported on the development of a reference material for the quality control of BAA determination in urine. In their investigations they also analyzed 4 urine samples of workers exposed to EGBE. The conjugate fraction ranged between 39% and 98% with a total excretion of BAA in the range of 257 to 345 mg/l.

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### **10.2 Exposure and effects**

Most of the studies on the relationship between external and internal exposure have already been presented in the BAT Documentations of 1996 and 2009. Hung et al. (2011) reported on a new study on the biomonitoring of 80 workers employed in bicycle manufacturing partly exposed to EGMBE. On the first and fifth day of the working week both the air exposure and the excretion of BAA in urine after hydrolysis were investigated. The workers examined consisted of a higher exposed group (n = 31), a lower exposed group (n = 25) and a control group without direct contact with EGBE (n = 24). The concentration levels of EGBE at the workplace were  $1.89 \pm 0.25 \text{ ml/m}^3$  (first day) and  $1.57 \pm 0.21 \text{ ml/m}^3$  (fifth day) for the higher exposed workers and the EGBE concentration levels for the lower exposed group were in the range of 0.07 to  $1.07 \text{ ml/m}^3$ . Before the first shift the BAA excretion levels of the higher and lower exposed groups were  $88.1 \pm 15.6 \text{ mg/g creatinine}$  and  $20.1 \pm 6.5 \text{ mg/g creatinine}$ , after the first shift the values were  $446.8 \pm 84.5 \text{ mg/g creatinine}$  and  $43.9 \pm 16.7 \text{ mg/g creatinine}$ , respectively. Before the fifth day of the working week BAA excretion levels of  $161 \pm 30.3 \text{ mg/g creatinine}$  and  $26.3 \pm 9.8 \text{ mg/g creatinine}$  were measured, after the shift on that day the values were  $619.4 \pm 137.7 \text{ mg/g creatinine}$  and  $60.8 \pm 32.6 \text{ mg/g creatinine}$ , respectively.

### **10.3 Selection of the indicators**

Because of its high sensitivity and elimination behaviour the analysis of BAA concentrations in urine is the best parameter for the determination of occupational exposures to EGBE and EGBEA (see BAT Documentations 1996, translated; 2009, translated). In the studies available to date either only the free BAA or only the total concentration of free and conjugated BAA were determined. Because of the great variation in the fraction of conjugates these analytical data are not comparable. Therefore, as was done for other biological exposure parameters as well, determination and evaluation of the total urinary excretion of BAA after hydrolysis is recommended.

### **10.4 Methods**

For the determination of the total urinary BAA excretion, the urine has first to be subjected to hydrochloric hydrolysis. The urine volume used for the analysis is mixed with concentrated hydrochloric acid and heated for one hour to boiling (Sakai et al. 1994). Under these conditions the glutamine conjugate is transformed into free BAA.

Several tested methods for the determination of BAA in urine have been made available by the working group "Analyses in Biological Materials" (Angerer et al. 1994, translated; Göen et al. 2006, translated).

## 10.5 Background exposure

Fromme et al. (2013) investigated the excretion of the metabolites of various glycol ethers in the urine of 44 persons in Germany occupationally not exposed to these substances. BAA was detected in 52% of these samples. The median and the 95th percentile of the free BAA concentrations were 0.01 and 0.12 mg/l, respectively. Similar results were reported by other working groups (see Fromme et al. 2013). Thus, the BAA excretion in the general population is clearly below the occupational assessment value as well as the urinary BAA levels of occupationally exposed persons.

## 10.6 Evaluation of the BAT value

As already described in the BAT Documentation of 2009, the MAK value for EGBE from 2006 was based on irritation of the mucous membranes observed in the animal experiment. The BAT value is therefore not derived from the MAK value but takes into account systemic effects, especially haemolysis. Since the last BAT Documentation of 2009 no new data have been published which would make a review of the toxicological evaluation necessary. In the BAT Documentation from 2009 the systemic no observed adverse effect level (NOAEL) of 25 ml EGBE/m<sup>3</sup> is related to a urinary excretion of 100 mg BAA/L. Since the last Documentation only one new occupational-medical field study by Hung et al. (2011) has been published which presented BAA excretion levels and EGBE air levels. However, this study was not included in this evaluation due to very low EGBE exposure. As the BAA is excreted in the urine in large, though greatly varying portions, in conjugated form, the BAT value to be established includes total excretion after hydrolysis. The few occupational-medical and experimental studies in which the total excretion of BAA was determined, however, do not permit the derivation of a BAT value. Therefore, a conversion from the correlate of free BAA is made. The studies in which the conjugate fraction of the total amount of BAA excreted in urine was determined revealed a considerably wide variation of the conjugate fraction which is due to the exposure level and possibly also to different individual enzyme patterns. On average about half of the total BAA excretion is as conjugate (factor 2). However, several studies indicate that with higher exposure levels the capacity of the conjugate reaction will be exceeded and lower conjugate proportions will be the result (Doerfler et al. 1996; Rettenmeier et al. 1993).

Based on the evidence of a high variability of conjugate formation and due to the decrease in the proportion of conjugate with higher exposure levels a conversion factor of 1.5 is used for converting the BAT value for free BAA valid to date into a BAT value for the total concentration of free and conjugated BAA. Furthermore, the influence of diuresis shall be controlled by its relation to creatinine, as in the case of methoxyacetic acid.

Therefore, a **BAT value** of

**150 mg butoxyacetic acid (after hydrolysis)/g creatinine**

is established.

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Sampling should be at the end of exposure or end of shift; for long-term exposures at the end of the shift after several shifts.

This value also applies both for EGBE and EGBEA, because both substances are metabolized to BAA.

### 10.7 Interpretation of results

The BAT value for EGBE relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. As a rule, where urine samples are outside the limits, a repetition of the measurement in normally hydrated test persons is recommended (see BAT Documentation 2010, translated).

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Accepted by the Working Group: 20 February 2015