Addendum to 2-Butoxyethanol (Ethylene glycol monobutyl ether)

BAT (2008)	**100 mg butoxyacetic acid/l urine***
	200 mg butoxyacetic acid (after hydrolysis)/l urine*
	Sampling time: for long-term exposures: after several shifts
MAK value (2006)	**10 ml/m³ ≙ 49 mg/m³****
Absorption through the skin (1980)	H
Carcinogenicity (2006)	Carcinogen Category 4

* No longer valid. For updated values/classifications please refer to http://onlinelibrary.wiley.com/book/10.1002/9783527695539
** MAK value applies for the sum of the concentrations of ethylene glycol monobutyl ether and its acetate in the air.

8 Re-evaluation

The MAK values for 2-butoxyethanol (BE, ethylene glycol monobutyl ether) and 2-butoxyethyl acetate (BEAc, ethylene glycol monobutyl ether acetate) were reduced from 20 to 10 ml/m³ in 2006. This was justified by the mucosal irritation caused by BE. In addition, BE and BEAc were classified into category 4 of carcinogenic substances (Greim 2007, translated; Greim 2008). As new original literature and new summaries (ATSDR 1998; ECETOC 2005; Greim 2007, translated; NTP 2000; WHO 1998) are available, a revision of the biological tolerance value (BAT value) evaluated in 1995 has become necessary.

In the following Addendum, studies both with BE and with BEAc are presented. An assessment of the data on both is necessary, as BEAc is rapidly hydrolysed to BE, from which the critical metabolite butoxyacetic acid is formed. In addition the MAK value applies for the sum concentration of both substances in air.

8.1 Metabolism and toxicokinetics

8.1.1 Absorption

As described in the BAT Documentation of 1996 (see 1996 BAT Documentation, translated), both BE and BEAc are absorbed at the workplace via the airways and through the skin.

Individuals were either exposed by inhalation only or by whole body dermal exposure only to 50 ml BE/m³ for two hours. The results suggest that 75% BE is directly absorbed through the skin from the gaseous phase (Johanson and Boman 1991; see Documentation 1996, translated).

In contrast, Corley et al. estimated the amount of BE directly absorbed from the gaseous phase through the skin as being considerably lower with values between 1.8% and 6.4% (Corley et al. 1997). Unlike Johanson and Boman (1991), they used venous blood to analyze BE. They attributed the difference in results to the different methods of obtaining blood samples.

Jones et al. conducted studies with whole body exposure with and without respirators (Jones et al. 2003). They found that 11% of the total BE dose is absorbed through the skin from the gaseous phase under resting conditions. However, they pointed out that, at higher temperatures and with a higher humidity, higher relative amounts are absorbed through the skin from the gaseous phase.

Absorption of liquid BE through the skin was more efficient using aqueous BE solutions than with undiluted BE. Compared with an inhalation of 100 mg BE/m³ (about 20 ml/m³) for 8 hours, which corresponds to a pulmonary absorption of 346 mg (assuming a respiratory volume of 10 l/min and an alveolar retention of 72%), dermally absorbed BE amounts of 1 340 mg (50% BE), 926 mg (90% BE) and 263 mg (undiluted BE) can be calculated for a dermal exposure of 1 000 cm² skin lasting one hour (Jakasa et al. 2004).

8.1.2 Metabolism

By far the main part of the BE absorbed in the human organism is metabolized to butoxyacetic acid, whereby 16% to 64% of the butoxyacetic acid formed is eliminated as N-butoxyacetylglutamine in the form of a glutamine conjugate (see Documentation 1996, translated). Corley et al. (1997) and Jones and Cocker (2003) also reported that about 65% or 57% of the total elimination of butoxyacetic acid takes place in the form of a glutamine conjugate.

8.2 Critical toxicity

The critical toxicity is described in the MAK documentation (Greim 2007, translated). In male and female individuals exposed to BE, irritant effects to eyes, nose

and throat as well as a disturbed taste, headaches and vomiting were observed above 100 ml/m³ (WHO 1998).

A LOAEC of 31.2 ml BE/m³ was obtained in rats in an inhalation study lasting 2 years based on histopathological findings of nose irritation. A benchmark calculation for a 5% increase in incidence revealed a benchmark concentration of about 15 ml BE/m³. As the rat, unlike humans, breathes through the nose only, the 2-year inhalation study produced merely an increase in the incidence but not in the severity of the irritant effects, and it can also be assumed that humans do not react more sensitively than rats, the MAK value has been lowered to 10 ml/m³ (Greim 2007, translated).

Increases were observed in the incidence of benign and malignant phaeochromocytomas in the adrenal cortex of female rats, in the incidence of liver cell carcinomas and haemangiosarcomas in the liver of male mice and in the incidence of squamous cell papillomas of the forestomach (combined with a concentration-dependent increase in ulcers and epithelial hyperplasia) of female mice after inhalative exposure to BE for two years. This has resulted in a classification in Category 4 for carcinogenic substances (Greim 2007, translated).

The main systemic adverse effects of BE are on the haematopoietic system (haemolytic effects), followed by possible teratogenic and testicular effects. In addition, effects on the central nervous system, the liver and the kidneys were discussed (see Documentation 1996, translated).

8.3 Exposure and effects

Relationships between external and internal exposure

Most of the studies available on the relationship between external and internal exposure have already been described in the BAT documentation of 1996 (see Documentation 1996, translated). Together with the studies already commented on, the more recent studies published since then are given in Table 1 (experimental studies) and Table 2 (studies with occupational exposure).

Only relatively low glycol ether concentrations were found at the different workplaces. The highest measured individual value was 7.3 ml/m³ (Angerer et al. 1990), the highest mean value 1.7 ml/m³ (Sakai et al. 1993) (see Documentation 1996, translated). Higher concentrations could also not be found in the new studies (ACGIH 2007; Haufroid et al. 1997; Laitinen 1998; Laitinen et al. 1998; Vincent et al. 1993). This means that, also after reducing the MAK value from 20 to 10 ml/m³, this concentration is not attained at the workplace. This is attributed to the low vapour pressure of the glycol ether, which prevents vaporization of large quantities of the substance into the air at the workplace. In an inhalation study with rats, that usually show higher sensitivity than humans, the NOAEC for haemolytic effects was 25 ml BE/m³.

Exposures at the level of the earlier and reduced MAK values are therefore only possible under experimental conditions (see Table 1). After exposure to 20 ml/m³

mainly by inhalation lasting two hours, both Dornow et al. (1990) and Johanson et al. (1986) determined almost identical amounts of butoxyacetic acid excreted with the urine with an average of 71 mg/g creatinine and 496 µmol/24 hours (about 65 mg/l). When extrapolated to an 8 hour working day, this corresponds to butoxyacetic acid amounts of 284 mg/g creatinine or 260 mg/l urine. At an exposure to 10 ml/m^3 and an extrapolation of the exposure time to 8 hours, the expected amount of butoxyacetic acid excreted with the urine would be about 140 mg/g creatinine or 130 mg/l by the end of this time. In a recently available study with exposure of individuals to 50 ml 2-butoxyethanol/m^3 by inhalation and through the skin for 2 hours under resting conditions, 70 mg free butoxyacetic acid/g creatinine and 164 mg total butoxyacetic acid/g creatinine were determined in the urine after hydrolysis (Jones and Cocker 2003). After exposure to 10 or 20 mg 2-butoxyethanol/m^3 for 8 hours, 56 or 112 mg free butoxyacetic acid/g creatinine and 131 or 262 mg total butoxyacetic acid/g creatinine were calculated. Although these values amount to only half of those determined by Johanson et al. (1986) and Dornow et al. (1990), the findings agree with a study by van Vlem (1987) (cited in ACGIH 2007). In this study, 34 and 48 mg butoxyacetic acid/g creatinine were excreted after exposure to 10.5 and 21 ml 2-butoxyethanol/m^3 for 4 hours, respectively. This corresponds to about 68 mg and 98 mg butoxyacetic acid/g creatinine after an 8-hour exposure to 10 ml and 20 ml 2-butoxyethanol/m^3, respectively.

If the excreted amounts of butoxyacetic acid measured at workplaces under very low exposure conditions (see Table 2) are extrapolated to concentrations of 10 or 20 ml/m^3, values are obtained which are also within this order of magnitude.

8.4 Selection of indicators

To estimate the internal exposure to BE and BEAc, the determination of free butoxyacetic acid in urine has proved useful (see Documentation 1996, translated).

As the extent of conjugation of butoxyacetic acid in urine varies considerably (Jones and Cocker 2003), the determination of hydrolysed butoxyacetic acid covers the total amount of butoxyacetic acid. It is therefore recommended that also the total excretion of butoxyacetic acid is determined after hydrolysis. Data from 48 exposed workers suggested that an about 57% of the total butoxyacetic acid is excreted in the conjugated form (Jones and Cocker 2003).

8.5 Methods

For the determination of free butoxyacetic acid in urine there is a tested method available by the Working Group "Analyses of Hazardous Substances in Biological Materials" (Angerer et al. 1994, translated; see Documentation 1996, translated).

To determine the total amount of butoxyacetic acid excreted with the urine, the urine must first be subjected to hydrochloric acid hydrolysis. For this, the same volume of concentrated hydrochloric acid is added to the volume of urine to be used for analysis and heated to boiling point for one hour (Sakai et al. 1994). Under these conditions, the glutamine conjugate is cleaved to the free butoxyacetic acid.

8.6 Background exposure

Many products contain glycol ether, e. g. BE as solvents, solubilizers, evaporation inhibitors etc., which are used both commercially and domestically. It may therefore be assumed that the general public comes into contact with BE at least occasionally, for example when renovating apartments, offices etc. In spite of this, only a few studies are available to date, investigating exposure of the general population to BE.

In a study with workers exposed occupationally to glycol, Sakai et al. also investigated 40 control persons not exposed to glycol ether occupationally (Sakai et al. 1993). The mean urinary butoxyacetic acid concentration of these persons was 80 ± 140 µg/g creatinine. A French working group investigated 109 persons employed in community administration with regard to possible exposure to glycol ether. Butoxyacetic acid was found in 68% of the investigated urine samples. The mean butoxyacetic acid concentration was given as 90 ± 90 µg/l urine (Ben-Brik et al. 2004). In a recent investigation of 29 persons not occupationally exposed to glycol ether, it was found that 14 individuals had butoxyacetic acid concentrations in their urine which were above the detection limit. The median value of the concentrations determined was 17 µg/l. The highest value was 63 µg/l (Göen et al. 2009).

In the studies cited, gas chromatographic-mass spectrometric methods were used with which detection limits between 10 and 50 µg butoxyacetic acid/l urine can be obtained. When using other, less sensitive analytical methods (for example GC/FID) butoxyacetic acid could not be detected in urine samples from the general population (Haufroid et al. 1997).

8.7 Evaluation

The MAK value was reduced as the result of mucous membrane irritation observed in an animal study. The BAT value, however, is intended to protect against systemic effects (especially haemolytic effects). A reduction of the BAT value as a result of the mucosal irritation is therefore not necessary. More recent animal studies showed that changes in haematological parameters occurred from 31 ml BE/m^3 after chronic exposure of rats. For the haemolytic effects a NOAEC of 25 ml BE/m^3 was obtained. In vivo and in vitro data indicate that rats are more sensitive with regard to the haemolytic effects than humans (Greim 2007, translated). At 20 ml

BE/m³ and the correlating BAT value of 100 mg butoxyacetic acid/l urine, no haemolytic effects are to be expected according to these recent studies. Also no other systemic effects are to be expected, as no prenatal toxicity was observed up to 100 ml BE/m³ and no effects on male reproductive organs occurred even at 125 ml/m³ (rats) or 250 ml/m³ (mice) (Greim 2007, translated). In addition, the correlation between 100 mg butoxyacetic acid/l urine and 120 ml 2-butoxyethanol/m³ is supported by a recently available study with individuals (Jones and Cocker 2003). Human studies on exposure and effects, however, are still not available.

The previous BAT value for free butoxyacetic acid of 100 mg butoxyacetic acid/l urine is therefore retained.*

This value applies both for BE and BEAc.

As described above, a considerable part of the 2-butoxyethanol absorbed is excreted in the 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 (Doerfler et al. 1996). Although the free butoxyacetic acid constitutes the ultimate toxic agent, it can nevertheless be useful to determine the total excretion of butoxyacetic acid when assessing the amount of 2-butoxyethanol actually absorbed. This can be performed after hydrochloric acid hydrolysis of the urine. According to the data by Jones and Cocker (2003), about twice as much total butoxyacetic acid than free butoxyacetic acid is excreted. For this total excretion, therefore, a further BAT value of

200 mg butoxyacetic acid (after hydrolysis)/l urine*

is established.

This value too applies for both BE and BEAc.

8.8 Interpretation of data

The excretion of butoxyacetic acid indicates specifically exposure to BE and BEAc respectively.

It has been found that butoxyacetic acid can also be detected in urine samples from the general population. This can most probably be attributed to the fact that glycol ether, especially also BE, is present in many consumer products. The highest expected concentration in the general population not handling glycol ethers occupationally should not exceed 0.5 mg butoxyacetic acid/l urine. Higher concentrations mean that 2-butoxyethanol is being handled occupationally.

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* No longer valid. For updated values/classifications please refer to http://onlinelibrary.wiley.com/book/9783527695539

The 2-butoxyacetic acid concentrations in urine found as background exposure of the general population are thus at least two orders of magnitude below the BAT value, which means that the assessment of occupational 2-butoxyethanol exposure is not confounded.

When the concentrations of butoxyacetic acid in urine exceed the BAT value of 100 mg free butoxyacetic acid/l or 200 mg total butoxyacetic acid/l, measures are to be taken to reduce the exposure of persons employed in this sector. This also applies when measurements in the ambient air indicate that the MAK value has been observed. BE is readily absorbed through the intact skin. This means that the butoxyacetic acid concentrations determined in the urine of workers should be used as a guide when taking occupational medical preventive measures.

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Table 1 Studies with experimental exposure of volunteers to 2-butoxyethanol (BE) and determination of 2-butoxyethanol or butoxyacetic acid (BAA) in urine or blood

Exposure conditions, Number of participants	Air	Urine		Blood		References
	BE [ml/m³]	BAA	BE	BE [mg/l]	BAA [mg/l]	
Inhalation 2 hours, 50 watts, 7 ♂	20	about 65 (25–116) mg/l		0.80		Johanson et al. 1986
Inhalation 2 hours, 10 ♂	20	71.3 ± 62 mg/g creatinine	0.11 ± 0.07 mg/g creatinine	0.32 ± 0.07		Dornow et al. 1990
Inhalation and dermal 2 hours, at rest, 2 ♂, 2 ♀	50	*6-10 hours:* 70 mg/g creatinine (free BAA), 164 mg/g creatinine (after hydrolysis)				Jones and Cocker 2003
Inhalation 4 hours, 3 participants		*0–4 hours:*				ACGIH 2007
at rest	21	48 mg/g creatinine				
at rest	10.5	34 mg/g creatinine				
30 W	10.5	38 mg/g creatinine				

Table 1 (Continued)

Exposure conditions, Number of participants	Air	Urine		Blood		References
	BE [ml/m³]	BAA	BE	BE [mg/l]	BAA [mg/l]	
Inhalation 2 hours, 50 W, 5 ♂	20				*1.0 hours*: 2.88 (2.57–3.41) *3.0 hours*: 5.83 (4.65–7.05) *4.9 hours*: 5.19 (2.44–7.46) *7.1 hours*: 3.71 (1.90–6.39)	Johanson and Johanson 1991
Inhalation (through the mouth) 2 hours, at rest, 4 ♂	50					Johanson and Boman 1991
22.6 °C, 29% relative air humidity				0.28 (0.21–0.32)		
32.9°C, 71% relative air humidity				0.40 (0.33–0.47)		
Dermal from gaseous phase 2 hours, at rest, 4 ♂	50					Johanson and Boman 1991
22.6 °C, 29% relative air humidity				0.74 (0.21–1.16)		
32.9 °C, 71% relative air humidity				1.42 (1.18–1.53)		
Dermal (via the finger) 12 × 2 hours, 5 ♂		24 hours: 12.51 mg/l (1.1–41.3 mg/l)				Johanson et al. 1988

Table 2 Occupational exposure of workers to 2-butoxyethanol (BE) or 2-butoxyethyl acetate (BEAc) with determination of butoxyacetic acid in urine (non-conjugated form) and 2-butoxyethanol in blood

Collective (n)	Exposure	Air	Urine	Blood	References
		BE or BEAc [ml/m³]	BAA [mg/l]	BE [mg/l]	
Printers (19 ♂)	MEAc, EEAc, BEAc	0.4 (< 0.1–1.5)	1.1 (0.5–3.8 mg)		Johanson et al. 1989
Mixing paints (formulation)	EE, EEAc, BE				Angerer et al. 1990
Production (12 ♂)		1.1 (< 0.1–8.1)	10.5 (0.6–30.3)	121.3 (< 5.0–570.0)	
Storage (3 ♂)		< 0.1	4.5 (1,1–8.8)	49.4 (< 5.0–143.1)	
Laboratory (2 ♂)		< 0.1	4.2 (3.9–4.4)	< 0.5	
Mixing paints (formulation)	EE, EEAc, BE				Söhnlein et al. 1993
		Monday:	*Start of shift*:		
Production (12 ♂)		0.5 (< 0.1–1.4)	0.2 (< 0.02–1.3)		
Storage (2 ♂)		< 0.1 (0.05–0.12)	0.09		
Laboratory (4 ♂)		< 0.1 (< 0.02–0.12)	0.04		
Foreman (1 ♂)		< 0.1	< 0.02		
		Tuesday:	*End of shift*:		
Production (12 ♂)		0.6 (< 0.1–1.0)	16.4 (0.8–60.6)		
Storage (2 ♂)		0.1 (< 0.1–0.2)	0.9 (0.4–1.4)		
Laboratory (4 ♀)		< 0.1	1.6 (0.1–5.1)		
Workers in preprocess (1 ♂)		< 0.1	0.9		

Table 2 (Continued)

Collective (n)	Exposure	Air	Urine	Blood	References
		BE or BEAc [ml/m³]	BAA [mg/l]	BE [mg/l]	
Workers (70)	BE, BEAc, gylcolether		mg/g creatinine:		Sakai et al. 1993
B (21)			0.67 ± 0.57 (0.0–2.0)		
C (19)			0.51 ± 0.32 (0.0–2.0)		
D (15)			0.12 ± 0.18 (0.0–1.5)		
E (6)			0.10 ± 0.12 (0.0–0.8)		
F (9)		0.64 ± 0.14 (0.4–0.8)	3.92 ± 2.75 (1.3–9.9)		
Control group (40)			0.08 ± 0.14 (0.0–0.6)		
Painters (6 ♂)	BE		194.28 (17.18–790.32)		Rettenmeier et al. 1993
Processing of dispersion paints (5)	BE	0.84 ± 0.69	27.0 ± 15.4		Knecht et al. 1990
Ceramics industry	BE				Söhnlein et al. 1993
(5 ♂)		< 0.1	6.46 ± 5.52 (< 0.02–12.52)		
(19 ♂, ♀)		< 0.1	0.65 ± 0.87 (< 0.02–2.61)		
Screen printing workers (8)	BE, BEAc	0.1–0.6	4.0–12.3 mg/g creatinine		Laitinen 1998
Screen printers (37 ♂, 15 ♀)	BE, BEAc	0.2–0.5	0–66.7 mg/g creatinine		Laitinen et al. 1998

Table 2 (Continued)

Collective (n)	Exposure	Air	Urine	Blood	References
		BE or BEAc [ml/m³]	BAA [mg/l]	BE [mg/l]	
Beverage production	BE, BEAc		mg/g creatinine:		Haufroid et al. 1997
Outside packing (21)		0.75 (0.37–1.27)	12.2 (0.3–51.4)		
Inside layer workers (10)		0.45 (0.15–0.69)	9.2 (0.6–20.4)		
Window cleaners	BE, BEAc		mg/g creatinine:		Vincent et al. 1993
New cars (7)		2.33 (0.10–7.33)	111.3 (12.7–371)		
Used cars (6)		0.36 (< 0.10–1.52)	6.3 (< 2.0–24.4)		
Office (16)		0.32 (< 0.30–0.73)	2.1 (2.0–3.3)		
Screen printing workers (5)	BE, BEAc	0.64	8.1 mg/l		van Vlem 1987; cited in ACGIH 2007

Abbreviations: BE: 2-butoxyethanol; BEAc: 2-butoxyethyl acetate; BAA: butoxyacetic acid; EE: 2-ethoxyethanol; EEAc: 2-ethoxyethyl acetate; MeAc: methoxyethyl acetate