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1,3-Butadiene – Addendum for re-evaluation of EKA and evaluation of BAR

Assessment Values in Biological Material – Translation of the German version from 2013

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BAR (2012)

400 µg 3,4-dihydroxybutyl mercapturic acid (DHBMA)[a]/g creatinine[c]

< 2 µg 2-hydroxy-3-butenyl mercapturic acid (MHBMA)[b]/g creatinine[c]

EKA (2012)

The following correlation between external and internal exposures is obtained:

Air		Urine	
1,3-Butadiene		3,4-Dihydroxybutyl mercapturic acid (DHBMA)[a]	2-Hydroxy-3-butenyl mercapturic acid (MHBMA)[b]
[ml/m³]	[mg/m³]	[µg/g creatinine]	[µg/g creatinine]
0.2	0.45	600	10
0.5	1.1	1000	20
1	2.3	1600	40
2	4.5	2900	80
3	6.8	4200	120

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

MAK value **not established**

Absorption through the skin –

Carcinogenicity (1998) Category 1

[a] synonym for N-acetyl-S-(3,4-dihydroxybutyl)cysteine

[b] synonym for N-acetyl-S-(2-hydroxy-3-butenyl)cysteine

[c] evaluated for non-smokers

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A BAT Documentation from 2006 is available, in which EKA (exposure equivalents for carcinogenic substances) were derived between the external exposure to 1,3-butadiene [106-99-0] and the urinary excretion of 3,4-dihydroxybutyl mercapturic acid (DHBMA, N-acetyl-S-(3,4-dihydroxybutyl)cysteine) at the end of exposure or at the end of a shift (translated in Csanády 2010). This Documentation is based on the improved database on background exposure and the relationships between the biomarkers and exposure in air obtained since the last establishment.

1 Selection of Indicators and Assay Materials

The most widely used parameters for biomonitoring 1,3-butadiene are the specific mercapturic acids 3,4-dihydroxybutyl mercapturic acid (DHBMA) and 2-hydroxy-3-butenyl mercapturic acid (MHBMA) in urine. There are no studies available for the elimination kinetics of butadiene mercapturic acids in humans. However, the results obtained by Albertini et al. (2001) indicate that workers at workplaces with an exposure above 1 ml 1,3-butadiene/m^3 still have clearly increased urinary DHBMA and MHBMA levels even at the start of the following shift. The half-lives are thus apparently so high that an accumulation can occur during the working week. The studies in which both metabolites were determined in urine during occupational exposure to 1,3-butadiene unanimously show that DHBMA is formed to a clearly greater extent than MHBMA. According to studies by Albertini et al. (2001), Boogaard et al. (2001) and van Sittert et al. (2000), the ratio between the additionally excreted quantities of DHBMA and MHBMA is in the range between 32 and 57. However, the parameter DHBMA in urine has the disadvantage that even in non-smokers occupationally not exposed to butadiene, a relatively high elimination occurs due to background exposure (see Section 4).

Further biomonitoring parameters of 1,3-butadiene, for which results from occupational–medical studies and on background exposure are available, are the covalent adducts to haemoglobin (Hb). This approach concentrates on the determination of the N-terminal adducts N-(2,3,4-trihydroxybutyl)valine (THBVal) and N-(monohydroxybutenyl)valine (MHBVal). In this case, the modified Edman degradation method is used, an established process in specialised laboratories worldwide (see Section 3). By determining the Hb adducts, the average exposure during the 120 days (average life of a red blood cell) preceding sampling is obtained. The studies by Albertini et al. (2001) and van Sittert et al. (2000) indicate that THBVal is formed to a clearly greater extent than MHBVal. Taking into consideration the different background exposure levels, the ratio between the formation of THBVal and MHBVal is in the range between 318 and 446. However, also for these parameters, it should be borne in mind that clearly higher background exposures exist for THBVal than for MHBVal (see Section 4).

Furthermore, there is also the possibility of demonstrating the presence of unchanged 1,3-butadiene in blood or in alveolar air (Lin et al. 2001). However, studies in test persons show that the elimination from the blood takes place so rapidly with half-lives of a few minutes that these parameters cannot be applied in occupational-medical practice (Csanády 2010).

Perbellini et al. (2003) report the possibility of demonstrating unchanged 1,3-butadiene in the urine of persons occupationally not exposed to 1,3-butadiene. The working group was able to find a significant (double logarithmic) correlation between the 1,3-butadiene concentration in urine and 1,3-butadiene concentrations in the blood of smokers. However, it remains unclear at present as to how this result is to be assessed for the biological monitoring of occupationally exposed persons in the light of the rapid elimination of 1,3-butadiene from blood.

2 Exposure and Effects

Table 1 gives a survey of 1,3-butadiene exposures in the air and the concentrations of DHBMA and MHBMA in the urine of occupationally exposed persons. Since the publication of the first documentation, the studies by Albertini et al. (2007), Fustinoni et al. (2004) and Vacek et al. (2010) have appeared. The study by Ammenheuser et al. (2001) is re-evaluated.

Ammenheuser et al. (2001) reported a study investigating the genotoxic effects in workers at a plant in South East Texas producing styrene-butadiene plastic. In accordance with earlier exposure data, the workers were divided into a low exposure and a high exposure group (25 and 24 workers, respectively). To measure exposure in each of the workers, a personal air sampler was carried throughout the entire shift and urine samples were obtained at the end of the shift, in which the concentration of DHBMA was analysed. The average air exposure was 0.15 ± 0.02 ml/m³ in the low exposure group and 1.48 ± 0.37 ml/m³ in the high exposure group. The DHBMA concentration in the post-shift urine was 585 ± 98 µg/g creatinine in the low exposure group and 2046 ± 348 µg/g creatinine in the high exposure group. By presenting a figure comparing the determined DHBMA levels of the workers with individual exposures to 1,3-butadiene in the air, the publication of Ammenheuser et al. (2001) also provides a view of the individual values. Thereby, the entire data presented in the figure indicate a positive correlation between the biomarkers and the air exposure. However, only comparatively low and thus implausible DHBMA values could be assigned to the two highest air exposure levels (at 5 ml 1,3-butadiene/m³). In their publication, the authors reported two cases, in which a concentration of 20.8 or 23 ml/m³ was determined in the air, which, however, were not included in the evaluation. One case involved a worker who had worn respiratory protection at least part of the time during a particularly high level of exposure at work; in the second case, a contamination of the air sampler with a liquid containing 1,3-butadiene was discovered. It can therefore not be excluded that influences of this kind were also present in the two implausible pairs of values. Figure 1 gives the individual values from the study by Ammenheuser et al. (2001) without these two value pairs. Also van Sittert et al. (2000) report in their publication on the occurrence of an implausibly high air value (at a level of 12.5 ml/m³) which was not included in the comparison of biomonitoring values and air values.

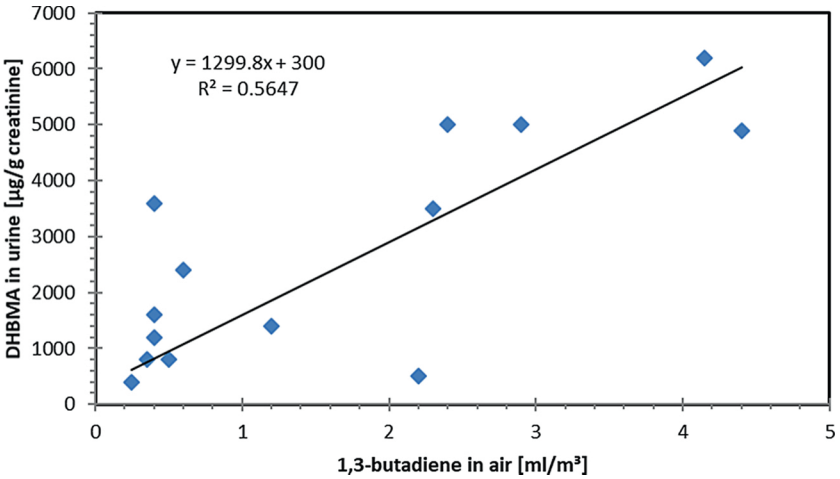

Fig. 1 Personal exposure to 1,3-butadiene in the air and DHBMA concentrations in the post-shift urine (data from Ammenheuser et al. (2001) without inclusion of two implausible value pairs measured at the highest air concentrations)

In a second study not discussed in the BAT Documentation of 2006, Fustinoni et al. (2004) investigated exposure to 1,3-butadiene in the air and the levels of various biomarkers of 1,3-butadiene in 42 workers (including 12 smokers) at a petrochemical plant engaged in the production or polymerization of 1,3-butadiene, as well as in 43 workers (including 11 smokers) at the same plant not having contact with 1,3-butadiene. The 1,3-butadiene exposure was recorded on three days for the workers in production and on one day for the internal controls by personal monitoring throughout the entire shift. For biological monitoring, the concentrations of 1,3-butadiene were determined in the exhaled air, in urine and blood, and the MHBMA and DHBMA concentrations in urine. The sampling of biological materials was carried out on the same day as the air measurements (in the exposed persons on the day of the final air measurement). Exhaled air and urine were obtained both before and after the shift. The average exposure to 1,3-butadiene in the air was 11.5 ± 35.8 µg/m³ (corresponding to 0.005 ± 0.016 ml/m³) for the exposed

persons and 0.9 ± 1.0 µg/m³ (corresponding to 0.0004 ± 0.0004 ml/m³) for the controls. No difference was found on comparison of the DHBMA concentration in the post-shift urine of the exposed persons (605 µg/l; 62–1643 µg/l) and controls (602 µg/l; 232–1009 µg/l). Also for the MHBMA concentrations in the post-shift urine of the exposed persons (10.5 µg/l; < 1.0–50.6 µg/l) and the controls (7.5 µg/l; < 1.0–21.8 µg/l) the difference was statistically not significant.

In the Czech collective occupationally exposed to 1,3-butadiene already described by van Sittert et al. (2000) and Albertini et al. (2001), Albertini et al. (2007) investigated the differences in 1,3-butadiene metabolism between women and men. In total, a collective of 104 persons (49 women and 55 men) was examined, out of which 51 (26 women and 25 men) were occupied in the administration of the plant (internal controls), 23 women were exposed to 1,3-butadiene in laboratory activities and 30 men were in the 1,3-butadiene polymerization unit.

For all workers, inhalative exposure to 1,3-butadiene was recorded during a study period lasting four months via 10 personal air measurements throughout the entire shift. In the final three days of the study period, the pre-shift and post-shift urine were sampled to determine the metabolites DHBMA and MHBMA. The air values were *not* determined simultaneously with the biomonitoring values. The average exposure to 1,3-butadiene in the air for the female control collective was given as 0.008 ± 0.005 mg/m³ (corresponding to 0.004 ± 0.002 ml/m³) and that for the male control collective as 0.007 ± 0.005 mg/m³ (corresponding to 0.003 ± 0.002 ml/m³). In the women exposed to 1,3-butadiene, the concentration was 0.397 ± 0.502 mg/m³ (corresponding to 0.18 ± 0.22 ml/in³). In the exposed men, the 1,3-butadiene respiratory exposure was determined as 0.808 ± 1.646 mg/m³ (corresponding to 0.36 ± 0.73 ml/m³). The urinary DHBMA concentration was 331.6 ± 284.9 µg/l in the female controls, 512.8 ± 272.1 µg/l in the male controls, 508.1 ± 597.4 µg/l in the laboratory assistants and 854.1 ± 567.0 µg/l in the men active in production. The MHBMA concentrations in urine were given as 8.3 ± 10.1 µg/l in the female controls, 14.9 ± 10.3 µg/l in the male controls, 19.2 ± 27.5 µg/l in the laboratory assistants and 47.9 ± 44.3 µg/l in the men active in production. A comparison of the double logarithmic correlations between the metabolite concentrations in urine and the 1,3-butadiene exposure in the air averaged over a period of four months carried out separately for the females and males revealed a significant difference in the axis intercept, but not for the slope of these functions, for both DHBMA and MHBMA. This result indicates a different background elimination of these two biomarkers in men and women. In the same collective, Vacek et al. (2010) investigated the effects on the formation of the Hb adducts THBVal in blood samples obtained in the study period described by Albertini et al. (2007). The THBVal concentrations were given as 181.1 ± 82.4 pmol/g globin in the female controls, 275.5 ± 264.5 pmol/g globin in the male controls, 224.5 ± 146.1 pmol/g globin in the laboratory assistants and 922.3 ± 381.9 pmol/g globin in the men active in production. A more differentiated consideration of the results revealed that the reasons for the differences in the exposures of the internal controls were mainly based on different levels of tobacco consumption. Whereas there was no significant increase in the THBVal concentration in the female smokers in the control collective (n = 6; 189.2 ± 48.5 pmol/g globin) compared with the female non-smokers (n = 19; 180.2 ± 93.3 pmol/g globin), a marked difference was found between the male smokers in the control collective (n = 7; 501.9 ± 436.6 pmol/g globin) and the male non-smokers (n = 15; 179.1 ± 40.4 pmol/g globin). As cause for this, a difference in the amounts of tobacco smoked between the male and female smokers examined is conceivable.

In a correlation analysis separated for females and males with regard to the relationship between THBVal concentration and exposure to 1,3-butadiene in the air, in this case, significant differences were found both for the axis intercept and for the slope. The authors evaluated this result also as being a sign of a difference between the sexes regarding the metabolism of 1,3-butadiene. The possible effect of a difference in the representativeness of the data for air exposure between the laboratory assistants and the production workers was not discussed.

The data for the DHBMA and MHBMA concentrations measured in the different studies under occupational 1,3-butadiene exposure are shown together with 1,3-butadiene air concentrations in Table 1.

Tab. 1 Exposure to 1,3-butadiene in the air and biomonitoring parameters in the post-shift urine of occupationally exposed persons (mean value ± standard deviation, unless otherwise stated)

Air	n	Urine		References
1,3-Butadiene [ml/m³]		DHBMA	MHBMA	
–	10	630 ± 190 µg/l	–	Bechtold et al. (1994)
occasionally	3	1390 ± 550 g/l	–	
3–4	7	3200 ± 1600 µg/l	–	
–	6	580 ± 191 µg/g creatinine	–	Ward et al. (1996)
0.03[a)]	5	355 ± 250 µg/g creatinine	–	
3.5[a)]	8	1690 ± 201 µg/g creatinine	–	
0.12	8	684 ± 176 µg/g creatinine	–	Ward et al. (1996)
0.21	7	596 ± 155 µg/g creatinine	–	
0.30	7	761 ± 245 µg/g creatinine	–	
0.3	19	694 ± 365 µg/l	–	Hallberg et al. (1997)
2.4	24	2429 ± 1877 µg/l	–	
1.0[a)]	7	600 µg/g creatinine	–	Hayes et al. (2000)
1.1[a)]	6	1500 µg/g creatinine	–	
3.5[a)]	3	700 µg/g creatinine	–	
45[a)]	9	8700 µg/g creatinine	–	
0.012	16	669 µg/l[b)]	4.2 µg/l[b)]	van Sittert et al. (2000)
4.3	5	2719 µg/l[b)]	97 µg/l[b)]	
0.01[a)/b)]	22	355 µg/l[b)]	1.6 µg/l[b)]	van Sittert et al. (2000)
0.17[a)/b)]	23	508 µg/l[b)]	3.6 µg/l[b)]	
0.49[a)/b)]	30	1479 µg/l[b)]	20 µg/l[b)]	
0.01[a)]	25	353 ± 157 µg/l	1.7 ± 1.5 µg/l	Albertini et al. (2001)
0.28[a)]	24	764 ± 728 µg/l	9.4 ± 13.0 µg/l	
0.77[a)]	33	4647 ± 6630 µg/l	120.2 ± 228.2 µg/l	
0.15	23	585 µg/g creatinine	–	Ammenheuser et al. (2001)
1.48	24	2046 µg/g creatinine	–	
–	10	1610 ± 600 µg/g creatinine	–	Fustinoni et al. (2002)
0.024	30	1800 ± 940 µg/g creatinine	–	
0.0004	43	602 ± 207 µg/l	7.5 ± 7.0 µg/l	Fustinoni et al. (2004)
0.005	42	605 ± 409 µg/l	10.5 ± 13.7 µg/l	
0.003	25 ♂	513 ± 272 µg/l	8.3 ± 10.1 µg/l	Albertini et al. (2007)
0.004	26 ♀	332 ± 285 µg/l	14.9 ± 10.3 µg/l	
0.176	23 ♀	508 ± 597 µg/l	19.2 ± 27.5 µg/l	
0.359	30 ♂	854 ± 567 µg/l	47.9 ± 44.3 µg/l	

[a)] the air values were *not* determined at the same time as the biomonitoring values
[b)] median values
n = number of examined persons

The data for the Hb adduct levels of THBVal and MHBVal determined in the different studies under occupational exposure to 1,3-butadiene are shown together with the 1,3-butadiene concentrations in the air in Table 2.

Tab. 2 Exposure to 1,3-butadiene in the air and 1,3-butadiene Hb adduct levels in occupationally exposed persons (mean value ± standard deviation)

1,3-Butadiene in air [ml/m³]	n	THBVal [pmol/g globin]	MHBVal [pmol/g globin]	References
0.1	7	–	0.04	Osterman-Golkar et al. (1996)
0.9	10	–	0.15	
0.01	22	95	0.2	van Sittert et al. (2000)
0.29	23	179	0.47	
0.82	30	717	2.2	
–	10 NS	35.3	–	Begemann et al. (2001)
0.014	17 NS	35.1	–	
diesel engine exhaust fumes	14 NS	43.5	–	
0.024	30	39.0 ± 9.9	–	Fustinoni et al. (2002)
0.01	25	94.77 ± 38.71	0.224 ± 0.205	Albertini et al. (2001)
0.28	24	178.73 ± 101.31	0.466 ± 0.452	
0.77	34	716.70 ± 425.72	2.230 ± 1.399	
0.004	26 ♀	181.1 ± 82.4	–	Vacek et al. (2010)
0.003	25 ♂	275.5 ± 264.5	–	
0.180	23 ♀	224.5 ± 146.1	–	
0.370	30 ♂	922.3 ± 381.9	–	

n = number of examined persons; NS = non-smokers

3 Analytical Methods

To determine the haemoglobin adducts of 1,3-butadiene (MHBVal and THBVal), a modified Edman degradation is carried out after separation of the erythrocyte fraction of the blood and isolation of the globin (Osterman-Golkar et al. 1996; Pérez et al. 1997). To isolate the globin, the protein fraction is precipitated from the obtained erythrocyte haemolysate using ethyl acetate, washed with organic solvents and subsequently dried. This globin is then subjected to the modified Edman degradation. Thereby, the alkylated N-terminal valine of the protein chain is cleaved off and converted to the corresponding pentafluorophenyl thiohydantoin derivative. The derivatives produced are extracted from the protein matrix using liquid-liquid extraction with diethylether and separated from interfering substances by subsequent washing steps.

In the case of the THBVal an additional acetylation of the hydroxy groups is then carried out (Pérez et al. 1997). Detection and quantification takes place using capillary gas chromatographic separation via tandem mass spectrometry in the NCI mode. For calibration, standards obtained either from the conversion of radioactively labelled valine-glycine-glycine-tripeptide and 1,2-epoxy-3-butene or diepoxybutane (Osterman-Golkar et al. 1996; Pérez et al. 1997) or a globin with known THBVal content are used (van Sittert et al. 2000).

In four studies (Albertini et al. 2001; Begemann et al. 2001; Fustinoni et al. 2002; Vacek et al. 2010), calibration of the THBVal analyses was done directly using the adduct-bearing amino acid (THBVal). As, in this case, the Edman degradation is not adequately reproduced, erroneous results may be obtained with this calibration method. These studies can therefore not be used for the evaluation.

To determine the mercapturic acids of 1,3-butadiene, methods using GC-MS technique (Bechtold et al. 1994; van Sittert et al. 2000) and, over recent years, increasingly procedures using LC-MS/MS are being used (Carrieri et al. 2009; Eckert et al. 2010; McDonald et al. 2004; Sapkota et al. 2006; Schettgen et al. 2009; Urban et al. 2003). A method for the determination of DHBMA and the MHBMA in urine based on the LC-MS/MS technique has also been published by the Working group "Analyses in Biological Material" (Scherer et al. 2008). Whereas the determination of DHBMA is largely unproblematic, errors can occur in the determination of MHBMA. On the one hand, attention has been drawn at a very early stage to the problems regarding the separation of the positional isomers and diastereomers of MHBMA using HPLC methods (Elfarra et al. 1995). It must be borne in mind that according to the information available to date, exclusively 2-hydroxy-3-butenyl mercapturic acid is formed in the human 1,3-butadiene metabolism, while calibration is often carried out with a standard substance containing at least two positional isomers (Eckert et al. 2010; Elfarra et al. 1995; Schettgen et al. 2009). It is not clear whether, as a result, any errors are produced. As a rule, it is assumed that the isomers in the standard substance are available in equal parts so that, for the calibration, the factor two is used.

In addition to this, after the chromatographic separation, the MHBMA peak may be superimposed by one or several interfering signals showing the same mass disintegration as MHBMA, so that they cannot be differentiated from the genuine MHBMA signal even in a tandem mass spectrometer. Methods that are not able to provide sufficient chromatographic resolution, therefore, can lead to false positive results or erroneous high concentrations (Eckert et al. 2011).

4 Background Exposure

In most of the occupational-medical studies listed in Section 2, the concentration of biomarkers of 1,3-butadiene exposure was analysed not only in workers exposed to 1,3-butadiene, but also in internal and partly external controls. Studies aiming at a determination of biomarkers in the general population occupationally not exposed to 1,3-butadiene, however, have not been carried out until recent years.

Sapkota et al. (2006) investigated the suitability of DHBMA and MHBMA for the assessment of environmental exposures to 1,3-butadiene. On the one hand, they analysed the 1,3-butadiene exposure of seven volunteers during a weekend they spent in the suburban areas, and during a working day in town with clear traffic influence as well as of seven workers in a toll booth. All study participants were non-smokers and lived in non-smoker families. The exposure to 1,3-butadiene in the air was determined using personal air samplers with an eight-hour duration for the toll collectors as well as for the weekend scenario and with a four-hour duration for the town centre scenario. From the toll collectors, up to six urine samples were obtained during the shift. In the weekend and town centre scenarios, all urine samples were collected before, during and directly after air measurement. The levels of DHBMA and MHBMA were analysed in all urine samples. The 1,3-butadiene exposure was determined as 1.22 ± 1.09 µg/m³ for the weekend scenario, 1.47 ± 0.73 µg/m³ for the town centre scenario and 2.88 ± 2.10 µg/m³ for the toll collectors. The DHBMA concentrations were determined as 306.5 ± 242.7 µg/l for the weekend scenario, 257.8 ± 133.2 µg/l for the town centre scenario and as 378.5 ± 196.0 µg/l for the toll collectors. The respective MHBMA concentrations were 6.8 ± 2.6 µg/l for the weekend scenario, 6.0 ± 4.3 µg/l for the town centre scenario and 9.7 ± 9.5 µg/l for the toll collectors. Therefore, even low exposures to 1,3-butadiene can lead to an increase in the 1,3-butadiene biomarkers DHBMA and MHBMA though these differences were, however, not statistically significant.

The authors also checked the association between the two biomarkers by means of a double logarithmic correlation. The following significant relationship was found:

$$\log_{\mathrm{DHBMA}}\,[\mathrm{ng/ml}] = 0.54 \times \log_{\mathrm{MHBMA}}\,[\mathrm{ng/ml}] + 4.56$$

where the data for $\log_{\mathrm{MHBMA}}$ cover a range from −1 to +4 (corresponding to a concentration range of 3–55 µg/l).

In several studies, Sarkar et al. (2008) investigated the effects of smoking cigarettes with activated carbon filters on the concentration of established biomarkers of tobacco smoke constituents such as MHBMA, 3-hydroxypropyl

mercapturic acid (3-HPMA) and S-phenyl mercapturic acid (S-PMA) in the smokers' urine compared with the levels when smoking conventional cigarettes or abstinence from tobacco. In the studies, 24-h urine samples (from 7 a. m. to 7 a. m. the following day) were obtained and analysed daily. To determine the effect of the smoking behaviour on the MHBMA concentration in urine, a group of 25 smokers habituated to 18 ± 5 cigarettes of the CC-6 type (conventional lit-end cigarettes) per day abstained from smoking tobacco after the first day of the study for the following 7 days. The MHBMA level dropped from the first day (2.70 ± 1.59 µg/g creatinine) initially to 0.48 ± 0.31 µg/g creatinine (first day of abstinence) and then to 0.17 ± 0.15 µg/g creatinine (second day of abstinence), attaining the background level on the third day of abstinence, which was determined as 0.09 ± 0.10 µg/g creatinine on the last day of the investigation. In a study (n = 20) investigating the effects of abstinence after consuming a cigarette brand with a higher tar content (CC-11), the MHBMA concentrations in the 24-h urine were 3.64 ± 3.12 µg/g creatinine (before abstinence), 0.57 ± 0.51 µg/g creatinine (1st day of abstinence), 0.07 ± 0.09 µg/g creatinine (2nd day of abstinence) and 0.06 ± 0.10 µg/g creatinine (7th day of abstinence).

Also in a population study (Roethig et al. 2009) the same research team investigated the effects of smoking on different biomarkers, including MHBMA and DHBMA. In a multicentre cross-sectional study with 4706 healthy, adult citizens from 31 states of the USA, 24-h urine samples were collected. Corresponding to their anamnestic data, the participants were assigned to a group of non-smokers (639 women and 438 men) and a group of smokers (2059 women and 1526 men). The latter was further divided into four groups corresponding to the tar contents of cigarette brands they were smoking. In the group of non-smokers, the average MHBMA excretion was 0.30 ± 0.66 µg/day and the average DHBMA excretion 391 ± 180 µg/day. In the smokers, the mean value for the MHBMA excretion was 3.61 ± 5.99 µg/day and for the DHBMA excretion 556 ± 293 µg/day. Statistically significant differences were found for the daily excretion of both parameters between male and female smokers. Whereas the daily MHBMA excretion was 4.00 ± 3.91 µg/day and the daily DHBMA excretion 634 ± 305 µg/day for male smokers, values of 3.26 ± 4.54 µg MHBMA/day and 487 ± 272 µg DHBMA/day were obtained for female smokers. When the sex differences in daily creatinine excretion with average values of 1.4 g/day for women and 1.7 g/day for men are taken into account, nearly identical values of 2.35 µg MHBMA/g creatinine and 373 µg DHBMA/g creatinine for male smokers and 2.33 µg MHBMA/g creatinine and 348 µg DHBMA/g creatinine for female smokers are obtained. Using the creatinine relationship to standardise the MHBMA and DHBMA excretion becomes plausible in the light of the fact that Roethig et al. (2009) also found significantly higher excretion values for smokers with a high body mass index (BMI ≥ 25 kg/m^2) compared with smokers with a lower BMI (< 25 kg/m^2).

Ding et al. (2009) carried out a study on the concentrations of six different mercapturic acids, including MHBMA and DHBMA, in the urine of 59 non-smokers and 61 smokers. The creatinine concentrations were in the range of 0.583 to 1.539 g/l urine, the MHBMA concentrations in the range of < limit of detection (LOD) to 122 µg/g creatinine for the non-smokers and in the range of < LOD to 59.7 µg/g creatinine for the smokers. The DHBMA concentrations were in the range of < LOD to 582 µg/g creatinine for the non-smokers and in the range of 166 to 1092 µg/g creatinine for the smokers. These differences between smokers and non-smokers were statistically significant for DHBMA but not for MHBMA.

In a way similar to that of Sarkar et al. (2008), Carmella et al. (2009) also investigated the effects of tobacco smoke abstinence on the biomarker concentrations of important carcinogenic tobacco smoke constituents, including DHBMA and MHBMA. In this study, especially smokers were included who had been smoking at least 10 cigarettes daily for at least one year and wanted to quit smoking. For the long-term study, 17 persons (11 women and 6 men) aged 23 to 58 years were selected. Before giving up smoking, the study participants were clinically examined and several 24-h urine samples obtained under standard smoking conditions (21.8 ± 6.7 cigarettes/day). After quitting smoking, the persons under tobacco smoke abstinence were clinically examined on days 3, 7, 14, 21, 28, 42 and 56 and 24-h urine samples collected on these days. In all urine samples several biomarkers, including MHBMA and DHBMA, were quantitatively analysed. Prior to abstaining from tobacco smoke, values of 66.1 ± 69.4 nmol MHBMA/day (corresponding to 15.3 ± 16.1 µg/day) and 1038 ± 514 nmol DHBMA/day (corresponding to 260 ± 129 µg/day) were found in the participants' urine. After quitting smoking, the excreted quantities dropped very rapidly so that

already on day three of abstinence, they were similar to those of non-smokers. On day 56 of abstinence, only 3.66 ± 2.41 nmol MHBMA/day (corresponding to 0.85 ± 0.56 µg/day) and 662 ± 248 nmol DHBMA/day (corresponding to 166 ± 62 µg/day) were excreted.

In one publication, an Italian working group presented a new analytical method for determining MHBMA in urine using LC-MS/MS and applying a polynominal calibration curve (Carrieri et al. 2009). They also presented, in addition to the validation data for the method, the results of the application of the method on the urine samples of 33 non-smokers. In these samples, DHBMA concentrations were in the range of 16–599 µg/l, with an average value of 166 µg/l.

Urban et al. (2003) reported on a powerful analytical method to determine MHBMA and DHBMA in urine using LC-MS/MS. Also in this publication, the results of applying the method to 24-h urine samples of 10 smokers and 10 non-smokers were presented. The MHBMA concentrations were given as 12.5 ± 1.0 µg/day (range: 7.0–18.0 µg/day) for the non-smokers and 86.4 ± 14.0 µg/day (range: 15.2–145.1 µg/day) for the smokers. The DHBMA concentrations were 459 ± 72 µg/day (range: 209–898 µg/day) for the non-smokers and 644 ± 90 µg/day (range: 116–1084 µg/day) for the smokers.

In addition, Schettgen et al. (2009) reported on an analytical method to determine the mercapturic acids of acrylonitrile and of 1,3-butadiene in urine using LC-MS/MS as technique. They also applied the method to urine samples of a total of 210 persons (198 men and 12 women) aged 19 to 80 years (median: 57.5 years) who had no occupational exposure to 1,3-butadiene. Of these, 73 persons were assigned to the group of non-smokers without any passive smoke exposure (group 1), 38 persons to the group of non-smokers with low passive smoke exposure (group 2), 18 persons to the group of non-smokers with high passive smoke exposure (group 3) and 81 persons were identified as active smokers. The following median DHBMA excretion values were reported for the different groups: 289 µg/l (range: 19.4–2500 µg/l) for group 1; 384 µg/l (range: 56.2–2008 µg/l) for group 2; 250 µg/l (range: 69.6–771 µg/l) for group 3 and 398 µg/l (range: 15.4–1959 µg/l) for the smokers. The MHBMA concentrations were below the detection limit of 2 µg/l in all samples from group 3 and in nearly all samples from groups 1 and 2 as well as in the majority of the samples from the smokers; 2.5 µg/l (group 1), 3.5 µg/l (group 2) and 17.5 µg/l (smokers) were given as maximum values. In accordance with these results, it seems that passive smoke exposure has a negligible effect on the concentrations of the biological exposure markers of 1,3-butadiene.

Eckert et al. (2011) reported a population study on the excretion of the metabolites of different alkylating substances, also including MHBMA and DHBMA. The study involved 94 persons who were occupationally not exposed to the investigated alkylators, including 1,3-butadiene, and whose spontaneous urine samples had creatinine concentrations in the range of 0.3 up to 3 g/l. The study included 57 women and 37 men aged 17 to 63 years (median: 30 years), of whom 40 persons (26 women and 14 men) could be assigned to the group of smokers and 54 persons (31 women and 23 men) to the group of non-smokers. The analysis of DHBMA in the urine samples revealed medians and 95th percentiles of 159 and 329 µg/g creatinine (range: 60–797 µg/g creatinine), respectively, for the non-smokers' group, as well as of 211 and 417 µg/g creatinine (range: 107–432 µg/g creatinine) for the smokers' group. This means that the DHBMA excretion of the smokers was only slightly, but statistically significantly higher than that of the non-smokers. The MHBMA level was below the detection limit of 5 µg/l in all the urine samples of the non-smokers and in the majority of the urine samples of the smokers. For the smokers, a 95th percentile of 9.5 µg/g creatinine and a maximum value of 11.9 µg/g creatinine were determined. The study also revealed a correlation between volume-related DHBMA levels and creatinine levels in the urine samples, for which reason the authors preferred to assess DHBMA excretion in relation to creatinine.

In Thailand, Arayasiri et al. (2010) carried out a biomonitoring study with 24 office policemen (non-smokers) and with 24 traffic policemen (non-smokers). The exposure to 1,3-butadiene was determined among others via MHBMA in the pre-shift and post-shift urine. The 1,3-butadiene exposure recorded by personal and stationary air sampling measurements was 0.40 ± 0.05 µg/m^3 in office policemen and 3.15 ± 0.16 µg/m^3 in traffic policemen. No increase in MHBMA concentration during a shift was found either in office or traffic policemen. Office policemen had a median

MHBMA concentration of 52.5 µg/g creatinine (17.0–125.4 µg/g creatinine) before the shift and 51.10 µg/g creatinine (18.9–106.7 µg/g creatinine) after the shift. The respective values for traffic policemen were 68.4 µg/g creatinine (19.2–146.8 µg/g creatinine) before the shift and 65.9 µg/l creatinine (23.1–199.7 µg/g creatinine) after the shift. However, all MHBMA values are classified as being implausibly high (see also Section 3).

Tables 3 and 4 summarise the concentrations of the 1,3-butadiene biomarkers in blood or urine of different population groups and test persons who had no occupational exposure to 1,3-butadiene.

Tab. 3 MHBVal and THBVal concentrations in the blood of persons occupationally not exposed to 1,3-butadiene (mean value ± standard deviation, unless stated otherwise)

Country	Year	Group	n	THBVal [pmol/g]	MHBVal [pmol/g]	References
Sweden	1994	NS/S	6/4	–	0.06	Osterman-Golkar et al. (1996)
Netherlands	1995	NS	12	–	< 0.1/– (< 0.1–1.2)[a)]	van Sittert et al. (2000)
		S	4	–	< 0.1/– (< 0.1–0.3)[a)]	
Czech Republic	1998	NS/S	16/9	94.8 ± 38.7	0.224 ± 0.205	Albertini et al. (2001)
Italy	2001	NS	10	35.3/– (22.7–44.9)[a)]	–	Begemann et al. (2001)
Czech Republic	2003	NS (♂)	15	179.1 ± 40.4	–	Vacek et al. (2010)
		NS (♀)	19	180.2 ± 93.3	–	
		S (♂)	7	501.9 ± 436.6	–	
		S (♀)	6	189.2 ± 48.5	–	

[a)] median/95th percentile (range)
n = number of examined persons; NS = non-smokers; S = smokers

Tab. 4 DHBMA and MHBMA concentrations in the urine of persons occupationally not exposed to 1,3-butadiene (mean value ± standard deviation, unless stated otherwise)

Country	Year	Group	n	DHBMA in urine	MHBMA in urine	References
USA	2005	NS	7	255/– (42.8–766) µg/l[a)]	6.1/– (3.7–11.1) µg/l[a)]	Sapkota et al. (2006)
		NS	7	244/– (46.3–513) µg/l[a)]	4.7/– (2.2–16.1) µg/l[a)]	
USA	2007	NS	25	–	0.09 ± 0.10 µg/g creatinine	Sarkar et al. (2008)
		NS	20	–	0.06 ± 0.10 µg/g creatinine	
		S	25	–	2.70 ± 1.59 µg/g creatinine	
		S	20	–	3.64 ± 3.12 µg/g creatinine	
USA	2008	NS	1077	239 µg/g creatinine[b)]	0.18 µg/g creatinine[b)]	Roethig et al. (2009)
		S	3585	327 µg/g creatinine[b)]	2.10 µg/g creatinine[b)]	
USA	2008	NS	59	105/– (< LOD–582 µg/g creatinine)[a)]	21/– (< LOD–122 µg/g creatinine)[a)]	Ding et al. (2009)
		S	61	510/– (166–1092 µg/g creatinine)[a)]	10/– (< LOD–59.7 µg/g creatinine)[a)]	
USA	2008	NS	17	97.7 ± 36.6 µg/g creatinine[b)]	0.50 ± 0.33 µg/g creatinine[b)]	Carmella et al. (2009)
		S	17	153 ± 75.9 µg/g creatinine[b)]	9.06 ± 9.51 µg/g creatinine[b)]	
Thailand	2006	NS	24	–	51.1/– (18.9–107) µg/g creatinine[a)]	Arayasiri et al. (2010)
Italy	2008	NS	33	166/– (16–599) µg/l[c)]	–	Carricri et al. (2009)
Germany	2003	NS	10	270 ± 42 (123–528) µg/g creatinine	7.4 ± 0.6 (4.1–10.6) µg/g creatinine	Urban et al. (2003)
		S	10	379 ± 53 (68–638) µg/g creatinine	50.8 ± 8.2 (8.9–85.4) µg/g creatinine	

Tab. 4 *(continued)*

Country	Year	Group	n	DHBMA in urine	MHBMA in urine	References
Germany	2008	NS	73	289/760 (19.4–2500) µg/l[a)]	< 2/< 2 (< 2–2.5) µg/l[a)]	Schettgen et al. (2009)
		S	81	398/1079 (15.4–1959) µg/l[a)]	< 2/8.6 (< 2–17.5) µg/l[a)]	
Germany	2010	NS	54	159/329 (60.2–797) µg/g creatinine[a)]	< 5/< 5 (< 5–< 5) µg/g creatinine[a)]	Eckert et al. (2011)
		S	40	211/417 (107–432) µg/g creatinine[a)]	< 5/9.5 (< 5–11.9) µg/g creatinine[a)]	

[a)] median/95th percentile (range)
[b)] values calculated on the basis of a creatinine excretion of 1.7 g/day; mean values and range are given
[c)] mean value/95th percentile (range)
LOD = limit of detection; n = number of examined persons; NS = non-smokers; S = smokers

5 Evaluation of the biological reference value (BAR)

There are no population studies available for the derivation of BARs for the two adducts of 1,3-butadiene with haemoglobin MHBVal and THBVal, but only results from a few persons without occupational contact to 1,3-butadiene who were examined as controls in occupational-medical studies (see Table 3). In addition, the few background data for THBVal are not congruent; the reason for this may be found in the different calibration procedures. Neither do the data available for MHBVal permit the establishment of a reference value. No BAR values are therefore established for these parameters.

On the other hand, numerous studies also including population studies, are available to derive BAR values for the renal excretion of the 1,3-butadiene metabolites DHBMA and MHBMA. However, the following fundamental aspects must be borne in mind when deriving a BAR from these studies:

- Owing to the uptake of 1,3-butadiene via tobacco smoke, smokers always have higher DHBMA and MHBMA concentrations in their urine.
- The DHBMA elimination in non-smokers obtained in all studies is considerably high; a physiological reason for this is assumed.
- On the other hand, MHBMA excretion is very low in non-smokers, thus indicating that this is a parameter of high specificity for exposure to 1,3-butadiene.
- When analysing MHBMA, a complete and careful separation of interfering components must be ensured, as this may otherwise produce erroneously high values.
- The studies by Albertini et al. (2007) and Eckert et al. (2011) indicate that there exists a very close relationship between the concentrations of mercapturic acids in urine and the creatinine concentration in urine.
- Owing to the different advantages of the parameters DHBMA (high sensitivity) and MHBMA (high specificity), BAR values are evaluated for both parameters.

To derive a BAR for DHBMA and MHBMA, the studies by Schettgen et al. (2009) and Eckert et al. (2011) seem particularly well suited, as both of these parameters were investigated in the urine of adults from the German general population. In both publications, the results for non-smokers and smokers are given separately. However, only in the publication of Eckert et al. (2011) were the results related to creatinine. In this study, the 95th percentile for DHBMA excretion in the non-smokers is given as 329 µg/g creatinine. The DHBMA values given by Schettgen et al. (2009) indicate a clearly greater variation and a 95th percentile of 760 µg/l. This greater variation can be ascribed to the fact that the values were not related to creatinine. In other studies, in which the DHBMA values were related to

creatinine (Carmella et al. 2009; Urban et al. 2003), the results agree very well with the data of Eckert et al. (2011). Based on the latter data,

a BAR of 400 µg 3,4-dihydroxybutyl mercapturic acid (DHBMA)/g creatinine

is established for **non-smokers**. Sampling should take place at the end of exposure or the end of the shift, for long-term exposures at the end of the shift after several shifts.

For the derivation of a reference value for MHBMA, the studies of Schettgen et al. (2009) and Eckert et al. (2011) are used. However, the quantification limits for the analytical determination of MHBMA were too high in both studies to determine the 95th percentile in the group of non-smokers. The studies in test persons by Sarkar et al. (2008) and Carmella et al. (2009) as well as the American population study by Roethig et al. (2009), which were carried out using more sensitive analytical methods, yielded average MHBMA concentrations of 0.1 µg/g creatinine, 0.5 µg/g creatinine and 0.2 µg/g creatinine for non-smokers or where abstinence from smoking tobacco was over a longer period. However, due to the possible selection bias, studies in test persons are not suitable for deriving a BAR for the general population. In the population study by Roethig et al. (2009), no 95th percentile values are given. In the study by Eckert et al. (2011), the MHBMA levels for all non-smokers were below 5 µg/g creatinine, whereas the 95th percentile for the MHBMA excretion in non-smokers was given by Schettgen et al. (2009) as < 2 µg/l. With an average creatinine concentration of 1.3 g/l in spontaneous urine samples and adhering to the creatinine relationship,

a BAR of < 2 µg 2-hydroxy-3-butenyl mercapturic acid (MHBMA)/g creatinine

is established for **non-smokers**. Sampling should take place at the end of exposure or the end of the shift, for long-term exposures at the end of the shift after several shifts.

6 Evaluation of EKA

Owing to the different advantages of the DHBMA (high sensitivity) and MHBMA (high specificity) parameters, EKA (exposure equivalents for carcinogenic substances) for both parameters are also evaluated.

For the derivation of exposure equivalents for the parameter DHBMA in urine and MHBMA in urine, numerous occupational-medical studies are available. Many of these studies, however, have the disadvantage that the exposure concentrations were not determined on the same day of the study as the biomonitoring parameters, which are important due to the short half-life (see Table 1). In addition, in several studies, the values for these biomonitoring parameters were not related to creatinine excretion. Only the study by Ammenheuser et al. (2001), by presenting the individual values for DHBMA excretion and the corresponding individual 1,3-butadiene exposure data, makes a detailed investigation and direct use for the derivation of an EKA possible. These data are shown in Figure 1. The regression analysis of these values, in which an average DHBMA excretion of 300 µg/g creatinine for occupationally not exposed persons was used as the y-intercept, produced the following linear relationship:

$$\mathbf{C_{DHBMA} = 1300 \times C_{BD} + 300}$$

where C_{DHBMA} represents the DHBMA concentration in urine [µg/g creatinine] and C_{BD} the 1,3-butadiene air concentration [ml/m^3].

Therefore, using this relationship, the following EKA are obtained for the parameter **DHBMA**:

Air		Urine
1,3-Butadiene		3,4-Dihydroxybutyl mercapturic acid (DHBMA)
[ml/m³]	[mg/m³]	[µg/g creatinine]
0.2	0.45	600
0.5	1.1	1000
1	2.3	1600
2	4.5	2900
3	6.8	4200

Because of a possible accumulation of DHBMA, sampling should take place at the end of exposure or end of shift, for long-term exposures at the end of the shift after several shifts.

The database for deriving exposure equivalents for the parameter MHBMA is less extensive than for DHBMA, as most occupational-medical studies exclusively concentrate on the main metabolite DHBMA. The simultaneously determined DHBMA and MHBMA levels in the study by Albertini et al. (2001) indicate that DHBMA is metabolically formed from the absorbed 1,3-butadiene at a 32-fold higher rate than MHBMA. By applying this factor to the slope of the abovementioned EKA between DHBMA excretion and 1,3-butadiene exposure in the air and considering that the MHBMA concentration in urine without exposure to 1,3-butadiene is below 2 µg/g creatinine, the following **EKA** are obtained for the parameter **MHBMA**:

Air		Urine
1,3-Butadiene		2-Hydroxy-3-butenyl mercapturic acid (MHBMA)
[ml/m³]	[mg/m³]	[µg/g creatinine]
0.2	0.45	10
0.5	1.1	20
1	2.3	40
2	4.5	80
3	6.8	120

Because of a possible accumulation of MHBMA excretion, sampling should take place at the end of exposure or end of shift, for long-term exposures at the end of the shift after several shifts.

7 Interpretation of Results

When interpreting the study results, particularly personal influence factors, for example a precise anamnesis of the smoker status, as well as non-occupational exposure to diesel engine emissions, are to be taken into account.

As the DHBMA is also formed on exposure to chloroprene (Eckert et al. 2013), a possible co-exposure to 1,3-butadiene and chloroprene should not be neglected and is to be taken into consideration where necessary when interpreting the results for DHBMA.

In the German studies, in the case of persons classified as "smokers" by anamnesis, the median values for DHBMA were only about 25% above those of non-smokers. However, the difference may be higher in heavy smokers. On the other hand, MHBMA is by far more affected by the smoking behaviour. According to the data from German population studies, the MHBMA concentration in heavy smokers can even exceed the value of 10 µg/g creatinine in individual cases, compared with concentrations of < 2 µg/g creatinine in non-smokers.

The possible indicators for a 1,3-butadiene biomonitoring presented in this documentation are a useful instrument for estimating exposure. For evaluation, in addition to the BAR values, the DHBMA and MHBMA concentrations can also be used, as obtained from the EKA correlation using the acceptance and tolerance values for 1,3-butadiene published in TRGS 910 of the Committee on Hazardous Substances (AGS 2014).

The BAR relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5 g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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