The MAK Collection for Occupational Health and Safety

Addendum to Benzene

Assessment Values in Biological Material – Translation of the German version from 2018

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Addendum to Benzene

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 derived biological reference values (BAR) and re-evaluated the exposure equivalents for carcinogenic substances (EKA) for the urinary benzene metabolites S-phenylmercapturic acid, t,t-muconic acid and benzene in 2016. Available publications are described in detail.

The existing exposure equivalents for carcinogenic substances (EKA) for the benzene metabolites were re-evaluated and extended especially to the low-exposure range. For the parameter benzene in urine, new EKA were established.

Taking results of studies into consideration with persons of the general population not occupationally exposed to benzene, with sufficient number of cases and current biomonitoring methods, biological reference values (BAR) of 0.3 µg S-phenylmercapturic acid/g creatinine, 150 µg t,t-muconic acid/g creatinine and 0.3 µg benzene/L urine were established. Sampling time is at the end of exposure or the end of the working shift.

Keywords

benzene; BAT value; EKA; exposure equivalent for carcinogenic substances; occupational exposure; biological tolerance value; toxicity

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EKA (2016) Correlations between external and internal exposure:

Air Benzene		Urine		
		S-Phenyl-mercapturic acid	t,t-Muconic acid	Benzene
[mL/m³]	[mg/m³]	[µg/g creatinine]	[µg/g creatinine]	[µg/L]
0.03	0.1	1.5*	-	0.5*
0.06	*0.2*	*3**	-	*0.8**
0.15	0.5	5	-	1.5
0.3	1.0	12	300	2.75
0.6	*2.0*	*25*	*500*	*5.0*
1.0	3.3	45	750	7.5
2.0	6.5	90	1200	12.5

* non-smokers only

Sampling time: end of exposure or end of shift

BAR (2016) **0.3 µg S-phenylmercapturic acid/g creatinine**

150 µg t,t-muconic acid/g creatinine

0.3 µg benzene/L urine

Sampling time: end of exposure or end of shift

MAK value (1971) **not established**

Absorption through the skin (1973) H

Carcinogenicity (1971) Category 1

The Commission classified benzene as a Category 1 carcinogen in 1971. The EKA correlations for the parameters benzene in blood and urinary phenol, published in 1984, were re-evaluated in 1993, and a correlation to the parameters benzene in blood as well as S-phenylmercapturic acid (SPMA) and t,t-muconic acid (t,t-MA) in urine was derived. In 2014, the correlation for benzene in blood was suspended

since the determination of benzene in blood has several shortcomings in practice, while the metabolites SPMA and t,t-MA constitute reliable parameters. Within the framework of this evaluation, the existing EKA correlations were re-evaluated and complemented, in particular in the low-dose range, and a new EKA correlation for the parameter urinary benzene was derived.

In addition, biological reference values (BAR) for SPMA, t,t-MA and benzene in urine were evaluated.

11 Re-evaluation of the EKA correlation

So far, the EKA correlations for SPMA and t,t-MA have been derived from studies by van Sittert et al. (1993) and Ducos et al. (1992) for a range of 0.3–6 mL benzene/m³ in air, and in consideration of a general background of 1 mg/L for t,t-MA (Lehnert and Greim 1996). As most national and international threshold values for airborne benzene concentrations are in the range of up to 1 mL/m³, it seems appropriate to adapt EKA correlations to this low-concentration range.

The evaluation included studies involving occupational exposure, measurement of airborne benzene concentrations and analysis of at least one of the following urinary biomarkers: SPMA, t,t-MA or unmetabolized benzene (see Table 11 of the Appendix). The derivation of EKA correlations in the low-dose range was exclusively based on data of non-smoker groups. Information on the smoking status was therefore obligatory for including these groups into the evaluation.

11.1 Evaluation of an EKA correlation for S-phenylmercapturic acid (SPMA)

As different analytical methods were applied in these studies, which did not yield comparable results, the next step was to consider only studies using a LC-MS/MS method for the evaluation of the SPMA correlation. Studies using an ELISA method for SPMA determination were excluded (Fracasso et al. 2010; Fustinoni et al. 2005). In the studies by Campagna et al. (2012) (LC-MS) and Ciarocca et al. (2012 a, b) (GC-MS), the results were below or near the detection limit of the method, which is why these studies were not taken into account in the evaluation.

Table 1 shows all the studies that meet the above-mentioned inclusion criteria and that used LC-MC/MS to measure the parameter.

A description of the essential information provided by these studies can be found in Table 11. A comparison of the studies by Manini et al. (2006) and Manini et al. (2008) shows that the SPMA concentrations differ by a factor of 5 for almost identical airborne benzene concentrations, which appears implausible. As the results of the study by Manini et al. (2008) are more in line with the results of the other studies, the study by Manini et al. (2006) was not taken into account in the evaluation. For the parameter SPMA, the results of Manini et al. (2008), Carrieri et al. (2010), Angelini et al. (2011) and Mansi et al. (2012) were thus used to establish a correlation in the range of 0.03–0.06 mL benzene/m³ air and the corresponding urinary SPMA concentration.

Table 1: Overview of studies in which the concentrations of benzene in air and of SPMA in the urine of non-smokers were analysed (urinary analysis by LC-MS/MS)

References	Benzene in air [mg/m³]	SPMA in urine [µg/g creatinine]	Value
Angelini et al. 2011	0.02055	0.35	median
	0.03248	0.69	maximum
	0.01398	0.21	minimum
Manini et al. 2006	0.006	2.14	geom. mean
	0.0077	4.01	68th percentile
Manini et al. 2008	0.0061	0.42	median
	0.0095	1.07	75th percentile
	0.0003	0.2	25th percentile
Maestri et al. 2005	0.0114	1.2	mean
	0.0327	2.1	68th percentile
Carrieri et al. 2010	0.0132	0.48	median
	0.0561	1.14	mean
Mansi et al. 2012	0.0368	0.84	mean

On the basis of this data, the following correlation can be established:

SPMA [µg/g crea] = 13.215 • airborne benzene [mg/m³] + 0.3225

Pearson's R = 0.662, p = 0.052

The resulting EKA correlation in the low-dose range for the biomarker SPMA is as follows (Table 2).

It is important to consider that the EKA correlation in the low-dose range is derived only for non-smokers. As benzene concentrations increase, the significance of an additional benzene uptake induced by tobacco smoke decreases. Therefore, the correlation derived by van Sittert et al. (1993) is still applied in the range from above 0.15 mL/m³ to 2 mL/m³ (Table 3).

Table 2: EKA correlation in the low-dose range for the biomarker SPMA

Benzene in air		SPMA in urine
[mL/m³]	[mg/m³]	[µg/g creatinine]
0.03	0.1	1.5*
0.06	0.2	3*

* non-smokers only

Table 3: EKA correlation derived by van Sittert et al. (1993) in the range from above 0.15 mL/m³ to 2 mL/m³ for the biomarker SPMA

Benzene in air		**SPMA in urine**
[mL/m³]	**[mg/m³]**	**[µg/g creatinine]**
0.15	0.5	5
0.3	1.0	12
0.6	*2.0*	*25*
1.0	3.3	45
2.0	6.5	90

11.2 Evaluation of an EKA correlation for t,t-muconic acid (t,t-MA)

Table 4 and Figure 1 show studies in which airborne benzene and urinary t,t-MA concentrations were determined in the low-dose range. Particularly in the low-dose range, the parameter t,t-MA is nonspecific and the validity of the parameter is limited.

In the low-dose range, the individual values are widely dispersed, so that no correlation can be derived for t,t-MA in the range below 0.3 mL benzene/m³ air.

Therefore, a correlation for the parameter t,t-MA is only established for benzene concentrations exceeding 0.3 mL/m³ air, and it is derived from a correlation to SPMA.

Bader et al. (2012, 2014) reported on the results of several studies in workers engaged in maintenance work at chemical plants for steam cracking and the synthesis of aromatic compounds. Within the framework of these studies, post-shift urine samples of the workers from two plants were analysed for the three urinary biomarkers t,t-MA, SPMA and benzene in 2011, with no distinction being made between smokers and non-smokers. Moreover, 79 urine samples from a control group not occupationally exposed to benzene were analysed in 2009. Results of benzene concentrations in workplace air were not available.

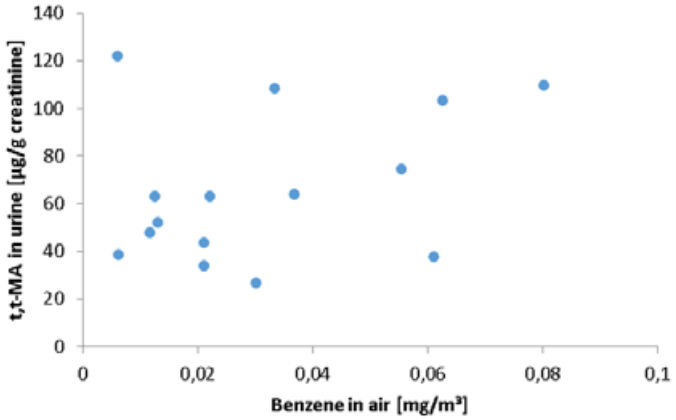

Figure 1 Correlation between the airborne benzene concentration and the concentration of t,t-muconic acid in the urine of non-smokers (studies from Table 4)

Table 4: Overview of studies in which the concentrations of benzene in air and of t,t-MA in the urine of non-smokers were analysed

References	Benzene in air [mg/m³]	t,t-MA in urine [µg/g creatinine]	Value
Carrieri et al. 2010	0.0553	74.7	mean
	0.013	52.1	median
Ciarrocca et al. 2012 a	0.0125	63.0	mean
	0.0116	47.8	mean
	< LOD (0.0016 µg/L)	32.0	mean
Fracasso et al. 2010	0.0625	103.5	median
	0.0801	109.6	median
	0.0333	108.5	median
Campagna et al. 2012	0.03	26.9*	median
Fustinoni et al. 2005	0.021	43.8*	median
	0.022	63.1*	median
	0.061	37.7*	median
Manini et al. 2006	0.006	122.0	mean
Manini et al. 2008	0.0061	38.6	median
Mansi et al. 2012	0.0368	63.9	mean
Carrer et al. 2000	0.021	33.8*	median

* The t,t-MA concentration given in µg/L in the original study was converted into µg/g creatinine based on a mean creatinine concentration of 1.3 g creatinine/L

Correlation analyses for the three biomarkers from a total of 372 urine samples (creatinine concentration between 0.3–3.0 g/L, all biomarkers above the respective detection limit) yielded the following results (Bader et al. 2012):

t,t-MA [mg/g crea] = 0.025 (0.001) • SPMA [µg/g crea] + 0.064 (0.019)

Spearman's R = 0.753, p < 0.001

After logarithmic transformation:

log t,t-MA [mg/g crea] = 0.574 (0.022) • log SPMA [µg/g crea] – 1.166 (0.031)

Pearson's R = 0.697, p < 0.001

Hence, the two biomarkers correlate very well. The linear evaluation yields a t,t-MA concentration of 689 µg/g creatinine for an SPMA concentration of 25 µg/g creatinine. Logarithmic plotting and analysis yields a t,t-MA concentration of 433 µg/g creatinine.

As for the correlation between t,t-MA and SPMA, the evaluations by Bader et al. (2014) under the same conditions (n = 172 samples) yielded the following results:

log t,t-MA [mg/g crea] = 0.619 (0.043) • log SPMA [µg/g crea] – 1.162 (0.036)

Pearson's R = 0.743, p < 0.001

An SPMA concentration of 25 µg/g creatinine thus corresponds to a t,t-MA concentration of about 500 µg/g creatinine (405–630 µg/g creatinine).

Taking the EKA correlation for airborne benzene and the urinary SPMA excretion as well as the results by Bader et al. (2012, 2014) as a basis, the resulting EKA correlation for t,t-MA is as follows (see Table 5).

11.3 Evaluation of an EKA correlation for urinary benzene

There are currently 4 studies in which urinary benzene was analysed in the low-dose range and in which the non-smoking status is specifically mentioned (Campagna et al. 2012; Fustinoni et al. 2005; Manini et al. 2006, 2008) (see Table 6).

Table 5: EKA correlations from the results by Bader et al. (2012, 2014)

Benzene in air		t,t-MA
[mL/m³]	[mg/m³]	[µg/g creatinine]
0.3	1.0	300
0.6	2.0	500
1.0	3.3	750
2.0	6.5	1200

Table 6: Studies measuring the urinary benzene concentration in non-smokers and airborne benzene concentration

References	Benzene in air [mg/m³]	Benzene in urine [ng/L]
Manini et al. 2008	0.0061	160
Campagna et al. 2012	0.03	267
Fustinoni et al. 2005	0.022	151
	0.061	342

Here again, the study by Manini et al. (2006) stands out as it yields other results at a similar air concentration. It is therefore again not taken into account in the evaluation. After excluding this study, correlation is good:

Urinary benzene [ng/L] = 3619.7 • airborne benzene [mg/m³] + 122.22

Pearson's R = 0.914, p = 0.086

The following EKA correlation for low-dose urinary benzene in non-smokers can be calculated on the basis of these studies (see Table 7).

At higher concentrations, there are no studies available regarding the correlation between airborne benzene and urinary benzene. If the urinary benzene concentrations are correlated with urinary SPMA or t,t-MA concentration (not with concentrations in air), the data obtained by Bader et al. (2012) yield the following correlations: (Pearson's R, all $p < 0.001$, after log transformation of the biomarker concentrations) (see Table 8).

Urinary benzene thus correlates with the two established biomarkers t,t-MA and SPMA both for volume-related measurement and after creatinine adjustment.

According to Bader et al. (2012), the correlation between the creatinine-adjusted concentrations of SPMA and benzene in urine is as follows:

log benzene [µg/g crea] = 0.797 (0.049) • log SPMA [µg/g crea] – 0.531 (0.035)

Hence, for an SPMA concentration of 25 µg/g creatinine, a benzene concentration of 3.8 µg/g creatinine can be expected. With a mean creatinine concentration of 1.3 g/L, this corresponds to approximately 4.94 µg benzene/L urine.

Taking into account the studies by Bader et al. (2012, 2014) as well as the reference to SPMA (not to air), the following EKA correlations for urinary benzene can be derived (see Table 9).

11.4 Summary

For the urinary biomarkers SPMA, t,t-MA and benzene, there are the following correlations between external and internal exposure (see Table 10).

Sampling should be performed at the end of exposure or at the end of the shift.

Table 7: EKA correlation for low-dose urinary benzene in non-smokers

Benzene in air		Benzene in urine
[mL/m³]	[mg/m³]	[µg/L]
0.03	0.1	0.48
0.06	0.2	0.83

Table 8: Data obtained by Bader et al. (2012) show correlations between urinary benzene concentrations and the urinary SPMA or t,t-MA concentration

	t,t-MA	t,t-MA	SPMA	SPMA
	[mg/L]	[mg/g creatinine]	[µg/L]	[µg/g creatinine]
Benzene in urine [µg/L]	0.562	0.462	0.673	0.553
Benzene in urine [µg/g creatinine]	0.434	0.503	0.615	0.644

Table 9: EKA correlations for urinary benzene

Benzene in air		Benzene in urine
[mL/m³]	[mg/m³]	[µg/L]
0.15	0.5	1.5
0.3	1.0	2.75
0.6	2.0	5.0
1.0	3.3	7.5
2.0	6.5	12.5

Table 10: EKA correlations for the urinary biomarkers SPMA, t,t-MA and benzene

Air		Urine		
Benzene		S-Phenylmercapturic acid	t,t-Muconic acid	Benzene
[mL/m³]	[mg/m³]	[µg/g creatinine]	[µg/g creatinine]	[µg/L]
0.03	0.1	1.5*	-	0.5*
0.06	*0.2*	*3**	-	*0.8**
0.15	0.5	5	-	1.5
0.3	1.0	12	300	2.75
0.6	*2.0*	*25*	*500*	*5.0*
1.0	3.3	45	750	7.5
2.0	6.5	90	1200	12.5

* non-smokers only

12 Derivation of Biological Reference Values (BAR)

Information on the background exposure is available for all three biomarkers (SPMA in urine, t,t-muconic acid in urine, benzene in urine). Table 12 of the Appendix provides an overview of the biomonitoring results for the background levels of these biomarkers in the general population.

12.1 Derivation of a Biological Reference Value for S-phenylmercapturic acid in urine

There are data available from several studies on the background levels of SPMA. If the focus is set on studies involving LC-MS/MS methods and sufficiently large sample sizes, in particular the studies by Schettgen et al. (2008 a) (n = 56 non-smokers), Schettgen et al. (2010 a) (n = 43 non-smokers), and Scherer et al. (2007) (n = 100 non-smokers) should be taken into account. In the study by Schettgen et al. (2010 a), the 95th percentile is 0.31 µg SPMA/g creatinine; in the study by Schettgen et al. (2008 a), it is 0.29 µg SPMA/g creatinine and in the study by Scherer et al. (2007), the 95th percentile is 0.5 µg SPMA/24h (≈ 0.3–0.5 µg/g taking into account the average creatinine excretion of 1.0–1.6 g/24h (Lehnert and Greim 2000). In the study by Campagna et al. (2012), the 75th percentile for the excretion of SPMA among 51 non-smokers from the general population was found to be approximately 0.15 µg SPMA/g creatinine. It is only the study by Bader et al. (2014 a) that specifies a 95th percentile of 3.3 µg SPMA/g creatinine for the urine samples of 69 non-smokers of a control group analysed by HPLC-MS within the framework of a workplace study (Bader 2017).

Based on the analytical results of the studies by Schettgen et al. (2008 a, 2010 a) and Scherer et al. (2007),

a BAR of 0.3 µg S-phenylmercapturic acid/g creatinine

is derived.

12.2 Derivation of a Biological Reference Value for t,t-muconic acid in urine

With respect to the parameter t,t-muconic acid, there are data available from several studies on the background exposure of persons non-occupationally exposed to benzene. Taking into account sufficiently large sample sizes, the key figures specified (mostly no 95th percentiles specified) and qualitative aspects, especially the studies by Aprea et al. (2008) (n = 264 non-smokers), Scherer et al. (2007) (n = 100 non-smokers) and Schettgen et al. (2010 b) (n = 33) are particularly conclusive. In the study by Aprea et al. (2008), the 95th percentile for the urinary excretion of t,t-muconic acid is found to be 143 µg/g creatinine; in the study by Schettgen et al. (2010 b), it is 135 µg t,t-muconic acid/g creatinine. Scherer et al. (2007) found a 90th percentile of 228 µg t,t-muconic acid/24h (≈ 143–228 µg/L).

In the study by Bader et al. (2014, 2017) a 95th percentile of 105 µg/g creatinine was found for the 69 non-smokers examined.

Based on the studies by Aprea et al. (2008), Scherer et al. (2007) and Schettgen et al. (2010 b),

a BAR of 150 µg t,t-muconic acid/g creatinine

is derived.

12.3 Derivation of a Biological Reference Value for benzene in urine

There are data available from few studies in which the concentration of the parameter benzene in urine was analysed as a measure of the background exposure of the non-occupationally exposed population to benzene. In the study by Campagna et al. (2014), the 95th percentile of urinary benzene in 86 non-smokers was found to be 311 ng/L. In the study by Campagna et al. (2012), the 75th percentile of urinary benzene in 51 non-smokers was 176 ng/L. Pezzagno et al. (1999) specified a mean value of 248.5 ng benzene/L urine with a standard deviation of 114.4 in 10 subjects. Fustinoni et al. (2005) determined a median of 133 ng benzene/L in the urine of 34 non-smokers. Taking into account the available study results and the sample sizes and taking in particular the study by Campagna et al. (2014) as a basis,

a BAR of 300 ng benzene/L urine

is derived.

Table 11: Study groups occupationally exposed to benzene

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Angelini et al. 2011	Policemen, total	70	19.33 µg/m³ (13.46–31.41)	0.38 (0.25–0.70)			Median (range)
	Indoor workers, total	40	2.95 µg/m³ (1.43–7.55)	0.15 (0.15–0.34)			Median (range)
	Policemen Non-smokers	50	20.55 µg/m³ (13.98–32.48)	0.35 (0.21–0.69)			Median (range)
	Indoor workers Non-smokers	25	2.20 µg/m³ (1.4–9.3)	0.15 (0.15)			Median (range)
Arayasiri et al. 2010	Policemen outdoor Non-smokers	24	38.62 µg/m³ (15.46–68.77)	0.45 (0.16–1.21)	83.00 (16.0–261)		Median (range), post-shift
	Policemen indoor Non-smokers	24	6.17 µg/m³ (3.57–14.14)	0.44 (0.11–0.86)	32.00 (5.0–100)		
Boogaard and van Sittert 1996	Workers in petrochemical industries	58	1 mL/m³ (3.25 mg/m³)	21 µmol/mol crea (44.4 µg/g crea)	1.5 mmol/mol crea (1885 µg/g crea)		Values calculated from regression line
	Control group Smokers	14		1.71 µmol/mol crea (3.61 µg/g crea)	0.046 mmol/mol crea (58 µg/g crea)		
	Control group Non-smokers	38		0.94 µmol/mol crea (2.0 µg/g crea)	0.029 mmol/mol crea (36 µg/g crea)		

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Campagna et al. 2012	Oil refinery workers	32	25.2 µg/m³	0.14 µg/L	52 µg/L	391	
	Oil refinery workers Non-smokers	19	30 µg/m³	< LOD	35 µg/L	267	
	Oil refinery workers Smokers	13	16 µg/m³	0.2 µg/L	92 µg/L	431	
	General population	65	9 µg/m³	0.2 µg/L	25 µg/L	126	
	General population Non-smokers	51	6 µg/m³	0.1 µg/L#	25 µg/L	120	
	General population Smokers	14	10 µg/m³	0.5 µg/L	23 µg/L	819	
Carrer et al. 2000	Office workers, Non-smokers	42	21 µg/m³		44 µg/L		
Carrieri et al. 2010	Petrochemical industry operators	29	AM: 0.014 145 samples Median: 0.003	AM: 2.83 133 samples Median: 0.89	AM: 100.98 133 samples Median: 68.49		Good correlation SPMA – air and t,t-MA – air
	Petrochemical industry operators Smokers	9	AM: 0.008 Median: 0.003	AM: 6.02 Median: 3.69	AM: 150.66 Median: 138.40		
	Petrochemical industry operators Non-smokers	20	AM: 0.017 Median: 0.004	AM: 1.14 Median: 0.48	AM: 74.72 Median: 52.15		

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Carrieri et al. 2012	Petrochemical workers	28	AM: 34.5 µg/m³ 173 samples Median: 9.2	AM: 1.52 Median: 0.54	AM: 104.2 Median: 68.6		similar group as in the study by Carrieri et. al. 2010, no significant influence of the GSTT1 null genotype on SPMA excretion
	Petrochemical workers Smokers	6	AM 22.4 µg/m³ 36 samples Median 7.0	AM: 3.94 Median: 3.53	AM: 124.5 Median: 120.2		
	Petrochemical workers Non-smokers	22	AM: 37.7 µg/m³ 137 samples Median: 10.3	AM: 0.88 Median: 0.34	AM: 98.8 Median: 56.9		
Ciarrocca et al. 2012 a	Traffic policemen, Smokers ♂	34		AM: 3.1 Median: 2.5 (82.3% < LOD)	AM: 95.9 Median: 74.0		
	Traffic policemen, Non-smokers ♂	62	AM: 12.5 µg/m³ Median: 9.45 µg/m³ TWA	AM: 2.9 Median: 1.5 (88.7% < LOD)	AM: 63.0 Median: 25.0		
	Police drivers, Smokers ♂	21		AM: 3.0 Median: 2.5 (90.4% < LOD)	AM: 100.1 Median: 85.0		
	Police drivers, Non-smokers ♂	22	AM: 11.6 µg/m³ Median: 12.3 µg/m³ TWA	AM: 3.1 Median: 2.5 (86.4% < LOD)	AM: 47.8 Median: 25.0 (68.2% < LOD)		

Table 11 (continued)

Authors	Study group	n	Benzene (air) [mL/m³]	S-Phenylmercapturic acid* [µg/g crea]	t,t-Muconic acid** [µg/g crea]	Benzene (urine) [ng/L]	Remarks
			Median				
	Roadmen, Control group Smokers ♂	53		AM: 2.7 Median: 2.5 (94.3% < LOD)	AM: 78.7 Median: 63		Rural areas
	Roadmen, Control group Non-smokers ♂	57	< 1.6 µg/m³	AM: 2.5 Median: 2.5 (98.2% < LOD)	AM: 32.0 Median: 25.0 (84.2% < LOD)		Rural areas, t,t-MA max 94 µg/g crea
Ciarrocca et al. 2012 b	Traffic policewomen, Non-smokers ♀	48	AM: 16.7 µg/m³ Median: 13.5 µg/m³ TWA	AM: 3.5 Median: 2.5	AM: 62.0 Median: 25.0		
	Police drivers, Non-smokers ♀	21	AM: 18.7 µg/m³ Median: 15.4 µg/m³ TWA	AM: 3.4 Median: 2.5	AM: 61.8 Median: 25.0		
	Roadwomen, Control group Non-smokers ♀	22	< 1.6 µg/m³	AM: 2.8 Median: 2.5	AM: 40.8 Median: 25.0		
Fracasso et al. 2010	General population Non-smokers	26	4.73 µg/m³	1.88	79.2		Non-smokers partly subjected to higher levels of exposure, ELISA for SPMA
	General population Smokers	25	7.80 µg/m³	2.30	88.6		

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
	Service station attendants Non-smokers	15	62.5 µg/m³	5.10	103.5		
	Service station attendants Smokers	13	29.0 µg/m³	7.20	127.00		
	Gasoline pump maintenance workers Non-smokers	12	80.1 µg/m³	2.01	109.6		
	Gasoline pump maintenance workers Smokers	9	9.5 µg/m³	1.05	65.90		
	Petrochemical industry operators Non-smokers	15	33.3 µg/m³	8.65	108.5		
	Petrochemical industry operators Smokers	18	22.8 µg/m³	8.60	139.0		

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Fustinoni et al. 2005	Genoa Control group Non-smokers	22	9 µg/m³	9 µg/L (≈ 6.9 µg/g crea)	51 µg/L (≈ 39.2 µg/g crea)		ELISA for SPMA
	Genoa Control group Smokers	27	9 µg/m³	13.7 µg/L (≈ 10.5 µg/g crea)	195 µg/L (≈ 150 µg/g crea)		
	Genoa Bus drivers Non-smokers	106	21 µg/m³	5.6 µg/L (≈ 4.3 µg/g crea)	57 µg/L (≈ 43.8 µg/g crea)		
	Genoa Bus drivers Smokers	47	21 µg/m³	9.3 µg/L (≈ 7.2 µg/g crea)	174 µg/L (133.8 µg/g crea)		
	Milan Control group Non-smokers	34	6 µg/m³	4.1 µg/L (≈ 3.2 µg/g crea)	33 µg/L (≈ 25.4 µg/g crea)	133	
	Milan Control group Smokers	24	6 µg/m³	8.0 µg/L (≈ 6.2 µg/g crea)	71 µg/L (≈ 54.6 µg/g crea)	331	
	Milan Traffic policemen Non-smokers	49	22 µg/m³	5.3 µg/L (≈ 4.1 µg/g crea)	82 µg/L (≈ 63.1 µg/g crea)	151	

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
	Milan Traffic policemen Smokers	28	22 µg/m³	9.1 µg/L (≈ 7 µg/g crea)	213 µg/L (≈ 163.8 µg/g crea)	753	
	Milan Gas station attendants Non-smokers	46	61 µg/m³	5.8 µg/L (≈ 4.5 µg/g crea)	49 µg/L (≈ 37.7 µg/g crea)	342	
	Milan Gas station attendants Smokers	32	61 µg/m³	7.5 µg/L (≈ 9.75 µg/g crea)	144 µg/L (≈ 110.8 µg/g crea)	1168	
Hoet et al. 2009	Petrochemical workers, Non-smokers	86	< 0.1–4.3	0.80	40	220	No precise air monitoring data provided, therefore not applicable for EKA
	Petrochemical workers, Smokers	24		2.02	60	410	

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Hopf et al. 2012	Process operators	15	GM: 0.01		GM: 1.70 µmol/L (≈ 185.8 µg/g crea)	GM: 1.70 nmol/L (132.8 ng/L)	Results not broken down by smoking habits
	Tank workers	10	GM: 0.15		GM: 3,01 µmol/L (≈ 329 µg/g crea)	GM: 1.70 nmol/L (132.8 ng/L)	
	Control group	18			GM: 1.76 µmol/L (≈ 192.4 µg/g crea)	GM: 0.86 nmol/L (67.2 ng/L)	
Jones and McCallum 2011	Tunnel construction	70	< 0.6–18	0.1–238,5 µmol/mol (0.21–504.6 µg/g crea)			Very wide exposure range over the course of time, no clear association between SPMA and air concentration
Lovreglio et al. 2010	Control group	31	4.3 µg/m³	0.22 (P95: 2.6)	59 (P95: 252)	120 (P95: 6.25)	no clear differentiation by smoking habits
	Fuel tank drivers	18	246.6 µg/m³	1.67	109	1490	
	Filling station attendants	23	20.9 µg/m³	0.56	89	210	

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Maestri et al. 2005	Control group Non-smokers	102		AM: 0.7 ± 0.6			
	Control group Smokers	134		AM: 3.0 ± 2.3			
	Workers exposed to benzene Non-smokers	231	11.4 µg/m³	AM: 1.2			
	Workers exposed to benzene Smokers	68	13.6 µg/m³	AM: 2.5			
Manini et al. 2006	Taxi drivers, Non-smokers	21	6.0 ± 1.7 µg/m³	GM: 2.14 ± 1.87	AM: 122.0 ± 70.3	GM: 440 ± 1790	Implausible results in comparison to Manini et. al. 2008, same method, same airborne exposure, measured values more than three times higher
	Taxi drivers, Smokers	16	5.6 ± 1.7 µg/m³	GM: 3.79 ± 1.5	AM: 154.4 ± 70.0	GM: 2580 ± 4230	
Manini et al. 2008	Traffic policemen, Non-smokers	80	6.1 (0.3–9.5) µg/m³	0.42 IQR (0.20–1.07)	38.6 IQR (31.7–51.6)	160 IQR (130–190)	
	Traffic policemen, Smokers	20		1.43	124.7	790	

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Manini et al. 2010	Gasoline pump attendants, Non-smokers	65		GM: 0.77	GM: 46.8		See above for study groups, additionally gasoline pump attendants, "similar" results without information being provided on airborne concentrations
	Gasoline pump attendants, Smokers	37		GM: 1.35	GM: 76.5		
Mansi et al. 2012	Petrochemical workers Non-smokers	103	36.8 µg/m³	AM: 0.84	AM: 63.87		
	Petrochemical workers Smokers	78		AM: 3.87	AM: 142.83		
	Control group Non-smokers	84		AM: 0.77	AM: 57.91		
	Control group Smokers	50		AM: 5.43	AM: 156.43		

Table 11 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[mL/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median				
Tunsaringkarn et al. 2011	Gasoline worker	33					No differentiation by smoking habits, no air monitoring
	Office workers	30					
Tunsaringkarn et al. 2013	Gasoline worker	102					No differentiation by smoking habits, no air monitoring
van Sittert et al. 1993	12 separate studies (chemical manufacturing plants, oil refineries, natural gas production plants)	4 to 156 each	1.0	AM: 12 (10–14)			SPMA mean (95% confidence interval)
			2.0	AM: 27 (24–30)			
			3.0	AM: 42 (38–46)			
			3.25	AM: 46 (41–50)			
			4.0	AM: 4,0 (52–62)			
Zhang et al. 2011	Shoe manufacture	44	AM: 44.8 mg/m³	AM: 656.8	AM: 10 774.92		Subjects were required to avoid smoking during the 1-week period prior to urine collection

GM = geometric mean; crea = creatinine; max = maximum; AM = arithmetic mean; IQR = interquartile range; LOD = limit of detection; TWA = time-weighted average

* if the SPMA concentrations in the original studies were given in µg/L, they were converted into µg/g crea based on a mean creatinine concentration of 1.3 g creatinine/L

** if the t,t-MA concentrations in the original studies were given in µg/L, they were converted into µg/g crea based on a mean creatinine concentration of 1.3 g creatinine/L

Median value for SPMA corresponds to LOD

The conversion factors for creatinine conversion (molecular weight 113.11 g/mol) are as follows:

SPMA (molecular weight = 239.29 g/mol)

µmol/mol • 2.11555 = µg/g

t,t-MA (molecular weight = 142.11 g/mol)

µmol/mol • 1.2564 = µg/g

Table 12: Background exposure of general population to benzene

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Aprea et al. 2008	General population	376	4.4–6.9		163.1		
	Smokers	111	5.5–7.6		236.9		
	Non-smokers	264	3.9–6.9		143.1		
	Non-smokers Men	128	5.5–6.6		117.8		Significant influence of gender in non-smoker group
	Non-smokers Women	136	3.5–7.0		220.0		
Bader et al. 2014; Bader 2017	Control group	79		5	150		Results not broken down by smoking habits
	Control group Non-smokers	69		3.3	105		Personal communication by M. Bader, 19 June 2017: recalculation from the non-smoker subgroup
B'Hymer 2011	Background exposure Smokers	5		AM: 0.4 µg/L (≈ 0.3 µg/g crea), max: 0.9 µg/L (≈ 0.7 µg/g crea)			
	Background exposure Non-smokers	6		< LOD			Paper on method development
Bevan et al. 2003	General population UK	426		7.0			SPMA measured using ELISA, no information provided on smoking habits

Table 12 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Boogaard and van Sittert 1996	Control group Smokers	14		AM: 1.71 µmol/mol crea (3.62 µg/g crea)	AM: 0.046 mmol/mol crea (58 µg/g crea)		
	Control group Non-smokers	38		AM: 0.94 µmol/mol crea (2.0 µg/g crea)	AM: 0.029 mmol/mol crea (36 µg/g crea)		
Campagna et al. 2012	General population	65	9	75th percentile: 0.3 µg/L (≈ 0.23 µg/g crea)	75th percentile: 44 µg/L (≈ 33.8 µg/g crea)	75th percentile: 226	
	General population Non-smokers	51	6	75th percentile: 0.2 µg/L (≈ 0.15 µg/g crea)	75th percentile: 41 µg/L (≈ 31.5 µg/g crea)	75th percentile: 176	
	General population Smokers	14	10	75th percentile: 1.5 µg/L (≈ 1.15 µg/g crea)	75th percentile: 101 µg/L (≈ 77.7 µg/g crea)	75th percentile: 2024	
Campagna et al. 2014	General population Non-smokers	86				311,5	
Chakroun et al. 2009	General population	182			360		Age dependence Significantly higher values compared to other studies
	General population Smokers	50			340		
	General population Non-smokers	132			310		

Table 12 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Ciarrocca et al. 2012 a	Roadmen, Control group Smokers ♂	53		AM ± SD: 2.7 ± 0.9 (94.3% < LOD)	AM ± SD: 78.7 ± 58.1		Rural areas
	Roadmen, Control group Non-smokers ♂	57	< 1.6	AM ± SD: 2.5 ± 0.1 (98.2% < LOD)	AM ± SD: 32.0 ± 17.2 (84.2% < LOD)		Rural areas
Ciarrocca et al. 2012 b	Roadwomen, Control group Non-smokers ♀	22	< 1.6	AM ± SD 2.8 ± 0.9 (2.5–5.0)	AM ± SD 40.8 ± 22.9 (25–95)		
Cocco et al. 2003	General population Smokers	13			Median: 50 (3–380)		
	General population Non-smokers	52			Median: 9 (2–1045)		No 95th percentile
Fracasso et al. 2010	General population Non-smokers	26	4.73	Median (range): 1.88 (0.30–9.62)	Median (range): 79.2 (3.00–460.50)		Non-smokers partly subjected to higher levels of exposure, no 95th percentile ELISA for SPMA
	General population Smokers	25	7.80	Median (range): 2.30 (0.50–10.08)	Median (range): 88.6 (13.30–445.00)		

Table 12 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Fustinoni et al. 2005	Genoa Control group Non-smokers	22	9	Median (range): 9 µg/L (0.2–182.2) (≈ 6.9 µg/g crea)	Median (range): 51 µg/L (< 10–181) (≈ 39.2 µg/g crea)		ELISA for SPMA
	Genoa Control group Smokers	27	9	Median (range): 13,7 µg/L (3.0–19.9) (≈ 10.5 µg/g crea)	Median (range): 195 µg/L (< 10–444) (≈ 150 µg/g crea)		
	Milan Control group Non-smokers	34	6	Median (range): 4.1 µg/L (0.2–12.5) (≈ 3.2 µg/g crea)	Median (range): 33 µg/L (< 10–1 089) (≈ 25.4 µg/g crea)	Median (range): 133 (< 15–409)	
	Milan Control group Smokers	24	6	Median (range): 8.0 µg/L (0.2–13.9) (≈ 6.2 µg/g crea)	Median (range): 71 µg/L (< 10–270) (≈ 54.6 µg/g crea)	Median (range): 331 (64–4615)	
Lovreglio et al. 2011	General population	137	< 2	3.49	188.8	3050	Results not broken down by smoking habits
Maestri et al. 2005	Control group Non-smokers	102		AM: 0.7 ± 0.6			
	Control group Smokers	134		AM: 3.0 ± 2.3			

Table 12 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Mansi et al. 2012	Control group Non-smokers	84		AM ± SD: 0.77 ± 1.45 (0.06–8.72)	AM ± SD: 57.91 ± 72.41 (3.63–475.71)		
	Control group Smokers	50		AM ± SD: 5.43 ± 5.65 (0.28–27.27)	AM ± SD: 156.43 ± 202.24 (21.47–1028.05)		
Melikian et al. 1993	General population Non-smokers	42			AM: 90 (< LOD–520)		
	General population Smokers	42			AM: 290 (20–1300)		
Pezzagno et al. 1999	General population Non-smokers	10			AM ± SD: 44.2 ± 34.0	AM ± SD: 248.5 ± 114.4	No 95th percentile
	General population Heavy smokers	10			AM ± SD: 149.9 ± 80.3	AM ± SD: 1782.5 ± 498.1	
Scherer et al. 2007	General population Non-smokers	100		90th percentile: 0.502 µg/24h	90th percentile: 228 µg/24h		
	General population Smokers	194		90th percentile: 4.229 µg/24h	90th percentile: 335 µg/24h		
Schettgen et al. 2010 a	General population Non-smokers	43		0.31			
	General population Smokers	72		4.63			

Table 12 (continued)

Authors	Study group	n	Benzene (air)	S-Phenylmercapturic acid*	t,t-Muconic acid**	Benzene (urine)	Remarks
			[µg/m³]	[µg/g crea]	[µg/g crea]	[ng/L]	
			Median		95th percentile		
Schettgen et al. 2010 b	General population Non-smokers	33		0.31 µg/L (≈ 0.24 µg/g crea)	176 µg/L (≈ 135.4 µg/g crea)		
	General population Smokers	21		4.02 µg/L (≈ 3.1 µg/g crea)	421 µg/L (≈ 323.8 µg/g crea)		
Schettgen et al. 2008 b	General population Non-smokers	15		0.12 (< 0.05–0.42)			
	General population Smokers	15		1.31 (0.24–3.33)			
Schettgen et al. 2008 a	General population Non-smokers	56		0.29			
	General population Smokers	72		6.04			

AM = arithmetic mean; crea = creatinine; LOD = limit of detection

*if the SPMA concentrations in the original studies were given in µg/L, they were converted into µg/g crea based on a mean creatinine concentration of 1.3 g crea/L

**if the t,t-MA concentrations in the original studies were given in µg/L, they were converted into µg/g crea based on a mean creatinine concentration of 1.3 g crea/L

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