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o-Toluidine – Evaluation of a BAR

Assessment Values in Biological Material – Translation of the German version from 2010

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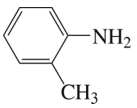
BAR (2009)	**0.2 µg o-toluidine/l urine**[a), b)] Sampling time: at the end of exposure or end of shift
Synonyms	1-Amino-2-methylbenzene 2-Aminotoluene 2-Methylaniline 2-Methylbenzenamine
CAS number	95-53-4
Structural formula	
Molecular formula	C_7H_9N
Molar mass	107.2 g/mol
Melting point	−14.7 °C (β-form)
Boiling point	200.2 °C
Vapour pressure at 20 °C	1.3 hPa
Density at 20 °C	1 g/cm³
MAK value	**not established**
Peak limitation	–
Absorption through the skin (1986)	H
Sensitization	–
Carcinogenicity (2006)	Category 1
Prenatal toxicity	–
Germ cell mutagenicity (2006)	Category 3 A

a) evaluated for non-smokers

b) No longer valid. For the current value see Klotz (2021).

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o-Toluidine and its salts occur as intermediate in the production of dyestuffs and pigments. o-Toluidine is furthermore used in plastic production and vulcanization processes and also in pharmaceuticals and pesticides (IARC 2000; NCBI 2020). The NOES (National Occupational Exposure Survey) showed that, between 1981 and 1983, 30 000 workers in the USA alone were potentially exposed to o-toluidine or its salts (CDC 1991), including workers from different branches of industry and fields of operation, for example laboratory workers, machine operators and cleaning personnel in the chemical industry. But also the general population is exposed to o-toluidine, as its presence could be demonstrated in the air, in water, soil samples, clothing, medication, foods, beverages, and in tobacco smoke. In 2006, due to the increased frequency of bladder tumours in occupationally exposed persons, o-toluidine was classified in Carcinogen Category 1 by the Commission (translated in Hartwig 2014). In 2008, o-toluidine was also classified by the IARC as human carcinogen (IARC 2010).

1 Metabolism and Toxicokinetics

1.1 Absorption and distribution

o-Toluidine is absorbed by inhalation or through skin contact (IARC 2000), whereby absorption through the skin from the gaseous phase can also take place. Apart from occupationally exposed persons, the general population is also exposed to o-toluidine detected in the air, in tobacco smoke, in food or in products manufactured using o-toluidine (IARC 2000; NCBI 2020).

In vitro investigations using concentrations relevant to workplace conditions demonstrated that the dermal flux of o-toluidine is not high, but that the absolute amount of 15% of the applied dose which penetrated within 24 hours is comparable with the dermal penetration rate of other aromatic amines with a good skin penetration (Lüersen et al. 2006; Wellner et al. 2005). In addition, using a skin protective cream, a far higher penetration through the skin can result (Korinth et al. 2006 b). o-Toluidine has therefore been designated with an "H" (Hartwig 2014; Henschler 1992).

1.2 Metabolism

The metabolism of o-toluidine was described in the MAK Documentation from 1986 (translated in Henschler 1992; see also OECD 2004). The toxicity of o-toluidine arises from a metabolic activation that can result in the formation of methaemoglobin (MetHb), haemoglobin- and DNA adducts. In this context, the most important reaction is N-hydroxylation.

In the erythrocyte, hydroxylamine is metabolised to nitrosobenzene, thereby forming methaemoglobin. Through the binding of the nitroso function to cysteine, haemoglobin (Hb)- and albumin adducts are formed. Due to their stability, these can be used in biomonitoring. In the target organ of its carcinogenic activity, the urinary bladder, hydroxylamine can be bound either directly (in acidic pH) or indirectly (after O-acetylation) – probably via a reactive nitrenium ion – to the DNA. The most frequent binding location in the DNA is, for aromatic amines, the C8 atom, followed by the exocyclic nitrogen atom of deoxyguanosin. Alternatively, aromatic amines can also be directly activated by cyclooxygenases to DNA-binding species not specified more closely.

1.3 Excretion

After absorption into the organism, o-toluidine is rapidly metabolised and excreted mainly with the urine. Exhalation as well as accumulation in the organs is low (Cheever et al. 1980; Son et al. 1980).

Significant differences in o-toluidine excretion between men and women were found as regards exposure of the general population to nitroaromatic compounds in the Federal Republic of Germany (Weiss and Angerer 2001). Men excrete more toluidine than women. This is particularly noticeable in the case of p-toluidine. This sex-specific

difference in excretion has already been observed in studies with rats (Chism and Rickert 1985; Rickert and Long 1981). The reasons for this sex-specific difference are not known to date.

2 Critical Toxicity

The acute toxicity of o-toluidine is based on methaemoglobin formation and the resultant reduced oxygen transport capacity of haemoglobin.

o-Toluidine is classified as being genotoxic and shows aneugenic effects. In rats and dogs, especially bladder tumours have been observed (Henschler 1992).

In humans, in various cohort studies with workers exposed to o-toluidine, the prevalence of bladder tumours was significantly above the expected level. In most of these studies, effects from exposure to other potential or demonstrated bladder carcinogens could not be completely excluded. For example, in the case of the largest cohort, a co-exposure to aniline could be confirmed in addition to o-toluidine exposure (Markowitz and Levin 2004; Ward et al. 1991).

On the basis of these studies, the Commission classified o-toluidine in Carcinogen Category 1 in 2006 (Hartwig 2014).

3 Exposure and Effects

Table 1 lists the studies in which the internal exposure of groups of persons exposed occupationally to o-toluidine were measured.

Tab. 1 Studies on o-toluidine exposure in occupationally exposed persons

Workplace, collective	o-Toluidine			References
	in air [µg/m³]	Hb adducts [pg/g Hb; *ng/l blood*]	in urine [µg/l urine]	
Rubber production				Ward et al. 1996
Workers exposed to o-toluidine and aniline (n = 28)	412 ± 366 (AM ± SD)			
Smokers pre-shift (n = 15)			14.3 ± 10.2 (AM ± SD)	
Non-smokers pre-shift (n = 28)			16.1 ± 33.0 (AM ± SD)	
Smokers post-shift (n = 15)			132.1 ± 153.1 (AM ± SD)	
Non-smokers post-shift (n = 27)			80.1 ± 94.0 (AM ± SD)	
Total pre-shift (n = 43)			15.4 ± 27.1 (AM ± SD)	
Total post-shift (n = 42)			98.7 ± 119.4 (AM ± SD)	
Non-smokers (n = 29)		41 028 ± 37 679 *6564 ± 6028* (AM ± SD)		
Smokers (n = 17)		40 494 ± 22 120 *6551 ± 3539* (AM ± SD)		
Total (n = 46)		40 830 ± 32 518 *6533 ± 5203* (AM ± SD)		

Tab. 1 *(continued)*

Workplace, collective	o-Toluidine			References
	in air [µg/m³]	**Hb adducts [pg/g Hb; *ng/l blood*]**	**in urine [µg/l urine]**	
Aromatic amine-based dye production (n = 342)	< 0.5 ml/m³ *< 2.2* (AM)		< 0.3–1.7 ppm (range) *< 0.3–1.7* (range) measurement in 1948!	Ott and Langner 1983
Pre-shift (n = 46)			18 ± 27 (AM ± SD)	Stettler et al. 1992; Teass et al. 1993
Post-shift (n = 46)			104 ± 111 (AM ± SD)	
Occupational exposure				Korinth et al. 2006 a
Healthy skin, smoker	58.29		74.83	
Mild erythema, smoker	93.93		242.88	
Burns, non-smoker	32.73		64.36	
Dishydrotic eczema, non-smoker	26.63		54.65	
Occupational exposure				Riffelmann et al. 1995
Smokers (n = 22)			0.6 ± 1.0 (AM ± SD)	
Non-smokers (n = 22)			0.4 ± 1.1 (AM ± SD)	
Fast acetylators (n = 25)			0.5 ± 1.1 (AM ± SD)	
Slow acetylators (n = 20)			0.8 ± 1.5 (AM ± SD)	
Occupational exposure and smokers				
Fast acetylators (n = 15)			0.5 ± 0.9 (AM ± SD)	
Slow acetylators (n = 7)			0.8 ± 1.0 (AM ± SD)	
Occupational exposure and non-smokers				
Fast acetylators (n = 9)			0.5 ± 1.3 (AM ± SD)	
Slow acetylators (n = 12)			0.3 ± 1.0 (AM ± SD)	
Occupational exposure to aniline and o-toluidine				Ruder et al. 1992
Smokers pre-shift (n = 19)			20.0 (AM)	
Smokers post-shift (n = 20)			135.6 (AM)	
Non-smokers pre-shift (n = 29)			17.5 (AM)	
Non-smokers post-shift (n = 32)			83.9 (AM)	

AM = arithmetic mean; SD = standard deviation
Values in *italics* are calculated.

Ward et al. (1996) investigated concentrations of o-toluidine in the urine and of o-toluidine adducts in the blood of 46 workers in chemical rubber production and 27 non-exposed persons were included as study controls. Individual air monitoring was carried out in 28 exposed workers. A mean concentration of o-toluidine in the air of 412 ± 366 µg/m³ was determined. The Hb adducts of o-toluidine were also determined in a number of these workers not described in greater detail (see Table 1).

At the end of the shift, significantly higher o-toluidine values in urine were found in smokers (132.1 ± 153.1 µg/l urine) than in non-smokers (80.1 ± 94.0 µg/l urine). However, no significant association between smoking habits and Hb adduct level could be found. The Hb adduct concentrations after the end of the shift correlated closely with o-toluidine values in urine, but not with o-toluidine values in the air.

Ott and Langner (1983) investigated the mortality of 342 workers from three dye factories (exposure to aromatic amines). The o-toluidine concentrations measured in the workplace air and in air samples from around the factories were consistently below the detection limit of 0.5 ml/m³ at that time, and the o-toluidine levels in urine, which however had been determined as far back as in 1948, were within a range from "below the detection limit" (at that time < 0.3 ml/m³) to 1.7 ml/m³ in workers producing thioindigo.

In their study, Stettler et al. (1992) and Teass et al. (1993) investigated the pre- and/or post-shift urine samples of 53 workers exposed to aniline and o-toluidine and 36 non-exposed workers. In 46 workers exposed to o-toluidine, the mean o-toluidine concentration after the shift was 104 ± 111 µg/l urine. No recorded parallel air measurement values are available. The authors stated that the 17 times higher concentration of o-toluidine in pre-shift urine samples (18 µg/l urine (arithmetic mean, AM)) in the exposed workers compared to the non-exposed (1.1 µg/l urine (AM)) suggests that o-toluidine accumulates during a working week. The increase in the urinary o-toluidine levels also in non-exposed workers (from 1.1 µg/l urine (AM) to 2.7 µg/l urine (AM)) can indicate that the o-toluidine concentrations in the air at the workplace are overall higher compared with the o-toluidine levels in the environment outside the factory, even if no direct contact with o-toluidine at the workplace occurred (see Table 2).

Tab. 2 o-Toluidine exposure in persons not directly occupationally exposed

Collective	o-Toluidine		References
	Hb adducts [ng/l blood]	in urine [µg/l urine]	
Control group from the rubber industry (workers who only had direct contact with vinyl chloride)			Ward et al. 1996
Smokers pre-shift (n = 10)		0.9 ± 0.7 (AM ± SD)	
Non-smokers pre-shift (n = 16)		1.3 ± 1.3 (AM ± SD)	
Smokers post-shift (n = 9)		2.8 ± 1.2 (AM ± SD)	
Non-smokers post-shift (n = 16)		2.8 ± 1.6 (AM ± SD)	
Total pre-shift (n = 26)		1.2 ± 1.1 (AM ± SD)	
Total post-shift (n = 25)		2.8 ± 1.4 (AM ± SD)	
Non-smokers (n = 17)	3518 ± 5581 pg/g Hb (AM ± SD) *563 ± 893 (AM ± SD)*		
Smokers (n = 10)	3510 ± 7064 pg/g Hb (AM ± SD) *562 ± 1 130 (AM ± SD)*		
Total (n = 27)	3515 ± 6036 pg/g Hb (AM ± SD) *562 ± 966 (AM ± SD)*		
Non exposed control group			Stettler et al. 1992; Teass et al. 1993
Pre-shift (n = 31)		1.1 ± 1.0 (AM ± SD)	
Post-shift (n = 31)		2.7 ± 1.4 (AM ± SD)	
Occupationally non-exposed (not defined in greater detail)			Riffelmann et al. 1995
Smokers (n = 8)		1.7 ± 1.6 (AM ± SD)	
Non-smokers (n = 8)		0.0 ± 0.0 (AM ± SD)	
Smokers pre-shift (n = 12)		1.0 (AM)	Ruder et al. 1992
Smokers post-shift (n = 11)		2.6 (AM)	
Non-smokers pre-shift (n = 20)		1.2 (AM)	
Non-smokers post-shift (n = 21)		2.8 (AM)	

AM = arithmetic mean; SD = standard deviation
Values in *italics* are calculated.

Korinth et al. (2006 a) investigated the respiratory and dermal absorption of o-toluidine in workers with contact to vulcanization accelerators containing o-toluidine. According to their interpretation of the results from four case reports, there was a relationship between skin condition (healthy to dishydrotic eczema) and the dermal absorption of o-toluidine.

Riffelmann et al. (1995) determined the Hb adducts in 45 male workers with contact to aromatic amines in three chemical factories (especially the synthesis and further processing of aniline and 4-chloroaniline; an exposure to o-toluidine is not reliably given). o-Toluidine in urine was determined; the sampling time is not known. The mean o-toluidine level in the urine of exposed smokers (0.6 ± 1.0 µg/l urine) was higher than in exposed non-smokers (0.4 ± 1.1 µg/l urine). Furthermore, a differentiation was made between slow and fast acetylators (slow: 0.8 ± 1.5 µg/l urine; fast: 0.5 ± 1.1 µg/l urine). Furthermore, in this study, the urine samples from an occupationally not directly exposed control group consisting of 16 men (8 smokers, 8 non-smokers) were also investigated (see Table 2).

Ruder et al. (1992) investigated the pre- and post-shift urinary o-toluidine levels of workers exposed to o-toluidine and aniline. The mean values are given in Table 1 (smokers post-shift: 135.6 µg/l urine; non-smokers post-shift: 83.9 µg/l urine). Furthermore, in 33 workers, the individual concentration of o-toluidine in the workplace air was determined. The individual values from air monitoring were not given, though it was pointed out that the results of the air measurements were clearly below the exposure limit of the Occupational Safety and Health Administration (OSHA) of 22 mg/m³ (5 ml/m³). The authors discuss absorption through the skin as an important exposure pathway that cannot be determined by air monitoring alone.

To summarise, it can be said that the data available for the relationship between external and internal exposure at the workplace are inadequate. Among other factors, this is because the internal exposure was determined in widely differing groups of occupationally exposed persons, without verification of the external exposure. Furthermore, no studies are available in which the internal o-toluidine burden (in blood or urine) was associated with acute health effects.

4 Selection of Indicators

Occupational exposure to o-toluidine can be verified by the determination of o-toluidine in urine whereby, especially due to the rapid excretion, the workplace exposure over the preceding 24 hours is recorded (see Section 1; Cheever et al. 1980).

In addition, the Hb adducts of o-toluidine can also be used for biomonitoring. These Hb adducts represent the mean internal burden over the preceding 120 days (the lifetime of erythrocytes, e.g. Stettler et al. 1992).

5 Analytical Methods

Weiss and Angerer (2004) established two routine methods for the biomonitoring of aromatic amines. For biomonitoring in cases of exposure to o-toluidine, determination of the unchanged o-toluidine or the conjugated o-toluidine excreted with the urine using capillary gas chromatography and electron capture detection is possible. In individual cases, GC/MS coupling is to be recommended for a differentiated determination of the different aromatic amines (Lewalter et al. 1994).

To determine the haemoglobin adducts, a method exists using gas chromatography/mass selective detection and negative chemical ionization (Lewalter et al. 2001).

As o-toluidine furthermore belongs to the methaemoglobin formers (MetHb), determination of the MetHb levels could also be carried out (Leng and Bolt 2016). Due to the instability of MetHb, however, this determination method can hardly be used in practice.

6 Background Exposure

6.1 Haemoglobin adducts of o-toluidine

In the study by Branner et al. (1998) a total of 103 pregnant women declaring themselves to be smokers (n = 25; Hb adducts of o-toluidine: 289 ± 25 pg/g Hb (46 ng/l blood)) or non-smokers (n = 78; Hb adducts of o-toluidine: 237 ± 65 pg/g Hb (38 ng/l blood)) were investigated. Bryant et al. (1988) investigated male blood donors from Turin, here also differentiating between the type of tobacco used in addition to smoking habits. In smokers using blond tobacco (n = 43), they found average o-toluidine Hb adduct concentrations of 290 ± 19 pg/g Hb (46.4 ng/l blood). Men stating they only smoked black tobacco (n = 18) attained average Hb adduct concentrations of 329 ± 22 pg/g Hb (56.2 ng/l blood). For non-smokers (n = 25), a mean value of 188 ± 19 pg/g Hb (30.1 ng/l blood) was given.

In the general population, Hb adducts of o-toluidine were found to range between 22.2 ng/l blood (95th percentile: 101 ng/l blood) in non-smokers (n = 154) and 25.0 ng/l blood (95th percentile: 79 ng/l blood) in smokers (n = 46) (detection limit: 0.5 ng/l blood) (Weiss 2005).

6.2 o-Toluidine in urine

Numerous studies have been published in which o-toluidine in urine was determined (see Table 3). The background exposures range between 0.03 to 172.93 µg/l urine for smokers and 0.03 to 34.2 µg/l urine for non-smokers.

Tab. 3 o-Toluidine in the urine or Hb adducts of o-toluidine in the blood of the general population without any occupational exposure

Collective	o-Toluidine		References
	Hb adducts [ng/l blood]	in urine [µg/l urine]	
General population total (n = 1004)			Kütting et al. 2009
Smokers (n = 145)		0.13 (AM) 0.03–172.93 (range) 0.03 (median) 0.41 (95th percentile)	
Non-smokers (n = 856)		0.1 (AM) 0.03–34.25 (range) 0.03 (median) 0.19 (95th percentile)	
General population smokers (n = 10)		0.204 ± 0.059 µg/24 h (AM)	Riedel et al. 2006
General population non-smokers (n = 10)		0.105 ± 0.026 µg/24 h (AM)	
Munich children total (n = 33)	632 ± 206 pg/g Hb (AM ± SD) *101 ± 33* (AM ± SD)		Richter et al. 2001
Without exposure to cigarette smoke (n = 15)	620 ± 206 pg/g Hb (AM ± SD) *99 ± 33* (AM ± SD)		
With exposure to cigarette smoke (n = 18)	642 ± 212 pg/g Hb (AM ± SD) *103 ± 34* (AM ± SD)		
Augsburg children total (n = 123)	598 ± 298 pg/g Hb (AM ± SD) *96 ± 48* (AM ± SD)		
Without exposure to cigarette smoke (n = 65)	621 ± 327 pg/g Hb (AM ± SD) *99 ± 52* (AM ± SD)		
With exposure to cigarette smoke (n = 58)	574 ± 262 pg/g Hb (AM ± SD) *92 ± 42* (AM ± SD)		

Tab. 3 *(continued)*

Collective	o-Toluidine		References
	Hb adducts [ng/l blood]	in urine [µg/l urine]	
Eichstätt children total (n = 64)	487 ± 295 pg/g Hb (AM ± SD) *78 ± 47* (AM ± SD)		
Without exposure to cigarette smoke (n = 39)	558 ± 328 pg/g Hb (AM ± SD) *89 ± 52* (AM ± SD)		
With exposure to cigarette smoke (n = 25)	376 ± 191 pg/g Hb (AM ± SD) *60 ± 31* (AM ± SD)		
Town population (n = 98)		0.108 (median) 0.356 (95^{th} percentile) < DL–0.851 (range)	Weiss 2005
Country population (n = 99)		0.093 (median) 0.385 (95^{th} percentile) < DL–1.660 (range)	
Total (n = 197)		0.099 (median) 0.382 (95^{th} percentile) < DL–1.660 (range)	
Non-smokers (n = 115)		0.085 (median) 0.263 (95^{th} percentile) < DL–1.660 (range)	
Passive smokers (n = 37)		0.087 (median) 0.158 (95^{th} percentile) < DL–0.209 (range)	
Smokers (n = 45)		0.206 (median) 0.541 (95^{th} percentile) < DL–0.838 (range)	
Non-smokers (n = 154)	22.2 (median) 101 (95^{th} percentile) < DL–5930 (range)		
Smokers (n = 46)	25.0 (median) 79 (95^{th} percentile) 10–110 (range)		
Total (n = 200)	22.6 (median) 82 (95^{th} percentile) < DL–5929 (range)		
Men, non-smokers		0.102 (median)	
Women, non-smokers		0.08 (median)	
General population (Mecklenburg-Vorpommern) (n = 40)		0.10 (median) 0.28 (95^{th} percentile) < DL–0.81 (range)	Schettgen et al. 2001
Non-smokers (n = 10)	0.03 ± 0.01 ng/g Hb (AM ± SD) *4.8 ng/l blood*		Stillwell et al. 1987
Smokers (n = 12)	0.10 ± 0.03 ng/g Hb (AM ± SD) *16.0 ng/l blood*		
Non-smokers (n = 5)	142 ± 85 fmol/g Hb (AM ± SD) *2.4 ng/l blood*		Falter et al. 1994
Smokers (n = 6)	310 ± 185 fmol/g Hb (AM ± SD) *5.3 ng/l blood*		

Tab. 3 *(continued)*

Collective	o-Toluidine		References
	Hb adducts [ng/l blood]	in urine [µg/l urine]	
Non-smokers (n = 78), only ♀	*237* ± 65 pg/g Hb *38 ng/l blood*		Branner et al. 1998
Smokers (n = 27), only ♀	289 ± 25 pg/g Hb *46 ng/l blood*		
Smokers: blond tobacco (n = 43)	290 ± 19 pg/g Hb (AM ± SD) *46.4 ng/l blood*		Bryant et al. 1988
Smokers: black tobacco (n = 18)	329 ± 22 pg/g Hb (AM ± SD) *52.6 ng/l blood*		
Non-smokers (n = 25)	188 ± 19 pg/g Hb (AM ± SD) *30.1 ng/l blood*		

AM = arithmetic mean; DL = detection limit; SD = standard deviation
Values in *italics* are calculated.

7 Evaluation

From the studies available, at present no correlation between external and internal exposure can be determined. The derivation of an EKA correlation is thus not possible. An (incomplete) relationship between air measurements and the presence of o-toluidine Hb adducts in blood is documented only in one study (Ward et al. 1996).

Also, the derivation of a health-based biological guidance value (BLW) is at present not possible, as no relevant health endpoints were investigated in the available studies which would make the derivation of a BLW appear sensible.

Therefore, it must be considered whether a biological reference value (BAR) can be derived for o-toluidine from the data of the general working population not occupationally exposed to the substance. The studies described in the preceding sections clarified that o-toluidine or its Hb adducts can be detected in biomonitoring studies of the general population and are decisively influenced by the smoking habits of the persons.

Hb adducts of o-toluidine The Hb adducts of o-toluidine have been determined in several studies. A study by Richter et al. (2001) cannot be taken as reference for the derivation of a BAR, as it comprises an investigation in children. The study by Branner et al. (1998) relates to a selected collective of pregnant women, which is also not useful for deriving a BAR. The studies by Bryant et al. (1988), Falter et al. (1994), Stillwell et al. (1987) as well as the results from the study by Weiss and Angerer (2004) remain to derive a BAR for the Hb adducts of o-toluidine. However, due to the small number of cases and the heterogeneous collectives, this parameter is not suitable for deriving a BAR at the moment.

o-Toluidine in urine In the study by Riedel et al. (2006), the analysis of o-toluidine relates to a 24-hour urine. Sampling in this way cannot be performed in practice. Thereby, the studies by Weiss (2005), Schettgen et al. (2001) and Kütting et al. (2009) are used to derive a BAR. Due to the number of cases investigated, the study by Kütting et al. (2009) is particularly relevant. Here, an o-toluidine value of 0.19 µg/l urine (95^{th} percentile) is given for non-smokers and a value of 0.41 µg/l urine for smokers. In the investigations by Weiss and Angerer (2004), the 95^{th} percentile of the results was 0.26 µg/l urine for non-smokers and 0.54 µg/l urine for smokers. Schettgen et al. (2001), in their sample population, report a 95^{th} percentile value of 0.28 µg/l urine in the general population (no differentiation between smokers and non-smokers).

Taking into account the cited studies, the following

BAR of 0.2 µg o-toluidine/l urine

evaluated for non-smokers, is established. Sampling should be carried out at the end of exposure or end of shift.

Note: It is necessary to perform hydrolysis, so this BAR is no longer valid. For updates please refer to Klotz (2021).

8 Interpretation

Determination of o-toluidine in urine means that changes in exposure can be detected fairly soon. Repeating the measurement at weekly intervals is possible.

The BAR relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0 g/l. In addition, 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 volunteers 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.

References

Bader M, Ochsmann E, Drexler H, Hartwig A, MAK Commission (2016) Addendum to creatinine as reference parameter for the concentration of substances in urine. BAT Value Documentation, 2010. MAK Collect Occup Health Saf 1(1): 266–268. DOI: 10.1002/3527600418.bbgeneral05e1715

Branner B, Kutzer C, Wickenpflug W, Scherer G, Heller WD, Richter E (1998) Haemoglobin adducts from aromatic amines and tobacco specific nitrosamines in pregnant smoking and non smoking women. Biomarkers 3(1): 35–47. DOI: 10.1080/135475098231354

Bryant MS, Vineis P, Skipper PL, Tannenbaum SR (1988) Hemoglobin adducts of aromatic amines: associations with smoking status and type of tobacco. Proc Natl Acad Sci USA 85(24): 9788–9791. DOI: 10.1073/pnas.85.24.9788

CDC (Centers of Disease Control) (1991) NIOSH alert: request for assistance in preventing bladder cancer from exposure to o-toluidine and aniline. MMWR Morb Mortal Wkly Rep 40(21): 353–354

Cheever KL, Richards DE, Plotnik HB (1980) Metabolism of ortho-, meta-, and para-toluidine in the adult male rat. Toxicol Appl Pharmacol 56(3): 361–369. DOI: 10.1016/0041-008x(80)90069-1

Chism JP, Rickert DE (1985) Isomer- and sex-specific bioactivation of mononitrotoluenes. Role of enterohepatic circulation. Drug Metab Dispos 13(6): 651–657

Falter B, Kutzer C, Richter E (1994) Biomonitoring of haemoglobin adducts: aromatic amines and tobacco-specific nitrosamines. Clin Investig 72(5): 364–371. DOI: 10.1007/BF00252829

Hartwig A (ed) (2014) o-Toluidine. MAK Value Documentation, 2007. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Wiley-VCH, Weinheim. DOI: 10.1002/3527600418.mb9553e4314

Henschler D (ed) (1992) o-Toluidine and o-toluidine hydrochloride. MAK Value Documentation, 1987. In: Occupational Toxicants, vol 3. VCH, Weinheim, 307–322. Also available from DOI: 10.1002/3527600418.mb9553e0003

IARC (International Agency for Research on Cancer) (2000) ortho-Toluidine. In: Some industrial chemicals. IARC-monographs on the evaluation of carcinogenic risks of chemicals to humans, vol 77. IARC, Lyon, 267–322. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono77.pdf, accessed 16 Oct 2020

IARC (International Agency for Research on Cancer) (2010) ortho-Toluidine. In: Some aromatic amines, organic dyes, and related exposures. IARC monographs on the evaluation of carcinogenic risks of chemicals to humans, vol 99. IARC, Lyon, 407–469. https://publications.iarc.fr/_publications/media/download/2958/04f67887be058cb7ae62b10572bf41e37643b15c.pdf, accessed 16 Oct 2020

Klotz K (2021) o-Toluidine – Addendum for re-evaluation of the BAR. Assessment Values in Biological Material – Translation of the German version from 2012. MAK Collect Occup Health Saf: Doc928. DOI: 10.34865/bb9553eoj21_1ad

Korinth G, Weiss T, Angerer J, Drexler H (2006 a) Dermal absorption of aromatic amines in workers with different skin lesions: a report on 4 cases. J Occup Med Toxicol 1: 17. DOI: 10.1186/1745-6673-1-17

Korinth G, Wellner T, Lüersen L, Herchenhan B, Angerer J, Drexler H (2006 b) Beschleunigung der dermalen Penetration von Kühlschmierstoffen und kanzerogenen Arbeitsstoffen durch Hautschutzcremes. Arbeitsmed Sozialmed Umweltmed 41: 106

Kütting B, Göen T, Schwegler U, Fromme H, Uter W, Angerer J, Drexler H (2009) Monoarylamines in the general population – a cross-sectional population-based study including 1004 Bavarian subjects. Int J Hyg Environ Health 212(3): 298–309. DOI: 10.1016/j.ijheh.2008.07.004

Leng G, Bolt HM (2016) Methemoglobin-forming substances. BAT Value Documentation, 2008. MAK Collect Occup Health Saf. DOI: 10.1002/3527600418.bb6253e1516

Lewalter J, Biedermann P, Angerer J, Müller G, Schaller KH (1994) Aromatic amines (Aniline, o-toluidine, m-toluidine, p-toluidine, 4-chloro-o-toluidine, 2,4-toluylenediamine and 2,6-toluylenediamine, 4-aminodiphenyl, 4,4′-diaminodiphenylmethane). Biomonitoring Method, 1994. In: Angerer J, Schaller KH, Greim H (eds) Analyses of Hazardous Substances in Biological Materials, vol 4. VCH, Weinheim, 67–105. Also available from DOI: 10.1002/3527600418.bi6253e0004

Lewalter J, Gries W, Angerer J, Sabbioni G (2001) Haemoglobin adducts of aromatic amines: aniline, o-, m- and p-toluidine, o-anisidine, p-chloroaniline, α- and β-naphthylamine, 4-aminodiphenyl, benzidine, 4,4′-diaminodiphenylmethane, 3,3′-dichlorobenzidine. Biomonitoring Method, 2000. In: Angerer J, Schaller KH, Greim H (eds) Analyses of Hazardous Substances in Biological Materials, vol 7. Wiley-VCH, Weinheim, 191–219. Also available from DOI: 10.1002/3527600418.biha_aame0007

Lüersen L, Wellner T, Koch HM, Angerer J, Drexler H, Korinth G (2006) Penetration of β-naphthylamine and o-toluidine through human skin in vitro. Arch Toxicol 80(10): 644–646. DOI: 10.1007/s00204-006-0095-z

Markowitz SB, Levin K (2004) Continued epidemic of bladder cancer in workers exposed to ortho-toluidine in a chemical factory. J Occup Environ Med 46(2): 154–160. DOI: 10.1097/01.jom.0000111602.76443.15

NCBI (National Center for Biotechnology Information) (2020) 2-Aminotoluene. PubChem annotation record. Source=HSDB. https://pubchem.ncbi.nlm.nih.gov/source/hsdb/2042, accessed 10 Nov 2020

OECD (Organisation for Economic Co-operation and Development) (2004) o-Toluidine, CAS-No. 95-53-4. SIDS initial assessment report. OECD, Paris

Ott MG, Langner RR (1983) A mortality survey of men engaged in the manufacture of organic dyes. J Occup Med 25(10): 763–768. DOI: 10.1097/00043764-198310000-00018

Richter E, Rösler S, Scherer G, Gostomzyk JG, Grübl A, Krämer U, Behrendt H (2001) Haemoglobin adducts from aromatic amines in children in relation to area of residence and exposure to environmental tobacco smoke. Int Arch Occup Environ Health 74(6): 421–428. DOI: 10.1007/s004200100243

Rickert DE, Long RM (1981) Metabolism and excretion of 2,4-dinitrotoluene in male and female Fischer 344 rats after different doses. Drug Metab Dispos 9(3): 226–232

Riedel K, Scherer G, Engl J, Hagedorn H-W, Tricker AR (2006) Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. J Anal Toxicol 30(3): 187–195. DOI: 10.1093/jat/30.3.187

Riffelmann M, Müller G, Schmieding W, Popp W, Norpoth K (1995) Biomonitoring of urinary aromatic amines and arylamine hemoglobin adducts in exposed workers and nonexposed control persons. Int Arch Occup Environ Health 68(1): 36–43. DOI: 10.1007/BF01831631

Ruder AM, Ward EM, Roberts DR, Teass AW, Brown KK, Fingerhut MA, Stettler LE (1992) Response of the National Institute for Occupational Safety and Health to an occupational health risk from exposure to ortho-toluidine and aniline. Scand J Work Environ Health 18(Suppl 2): 82–84

Schettgen T, Weiß T, Angerer J (2001) Biological monitoring of phenmedipham: determination of m-toluidine in urine. Arch Toxicol 75(3): 145–149. DOI: 10.1007/s002040100218

Son OS, Everett DW, Fiala ES (1980) Metabolism of o-[methyl-14C]toluidine in the F344 rat. Xenobiotica 10(7-8): 457–468. DOI: 10.3109/00498258009033781

Stettler LE, Savage RE, Brown KK, Cheever KL, Weigel WW, DeBord DG, Teass AW, Dankovic D, Ward EM (1992) Biological monitoring for occupational exposures to ortho-toluidine and aniline. Scand J Work Environ Health 18(Suppl 2): 78–81

Stillwell WG, Bryant MS, Wishnok JS (1987) GC/MS analysis of biologically important aromatic amines. Application to human dosimetry. Biomed Environ Mass Spectrom 14(5): 221–227. DOI: 10.1002/bms.1200140505

Teass AW, DeBord DG, Brown KK, Cheever KL, Stettler LE, Savage RE, Weigel WW, Dankovic D, Ward E (1993) Biological monitoring for occupational exposures to o-toluidine and aniline. Int Arch Occup Environ Health 65(1 Suppl): S115–S118. DOI: 10.1007/BF00381320

Ward EM, Carpenter A, Markowitz S, Roberts D, Halperin W (1991) Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. J Natl Cancer Inst 83(7): 501–506. DOI: 10.1093/jnci/83.7.501

Ward EM, Sabbioni G, DeBord DG, Teass AW, Brown KK, Talaska GG, Roberts DR, Ruder AM, Streicher RP (1996) Monitoring of aromatic amine exposures in workers at a chemical plant with a known bladder cancer excess. J Natl Cancer Inst 88(15): 1046–1052. DOI: 10.1093/jnci/88.15.1046

Weiss T (2005) Entwicklung und Anwendung analytischer Methoden zum biologischen Monitoring und biochemischen Effektmonitoring von aromatischen Aminen im Rahmen arbeits- und umweltmedizinischer Fragestellungen. Dissertation, Friedrich-Alexander-Universität, Erlangen

Weiss T, Angerer J (2001) Belastung der Bevölkerung der Bundesrepublik Deutschland durch amino- und nitroaromatische Verbindungen. Abschlussbericht (PUG U97009). https://pudi.lubw.de/detailseite/-/publication/34332-Belastung_der_Bev%C3%B6lkerung_der_Bundesrepublik_Deutschland_durch_amino-_und_nitroaromatische_Verbindun.pdf, accessed 14 Oct 2020

Weiss T, Angerer J (2004) Belastung der Bevölkerung der Bundesrepublik Deutschland durch nitroaromatische Verbindungen – Der Einfluss von Ernährung und Bekleidung. BWB 20007. https://pudi.lubw.de/detailseite/-/publication/28968-Belastung_der_Bev%C3%B6lkerung_der_Bundesrepublik_Deutschland_durch_nitroaromatische_Verbindungen_-_Der_E.pdf, accessed 14 Oct 2020

Wellner T, Lüersen L, Angerer J, Drexler H, Korinth G (2005) Die Hautpenetration von aromatischen Aminen. Arbeitsmed Sozialmed Umweltmed 40: 169–170