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Acrylamide – Addendum for re-evaluation of the BLW and evaluation of EKA and BAR

Assessment Values in Biological Material – Translation of the German version from 2012

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BAR (2011)

50 pmol N-(2-carbonamide ethyl)valine (AAVal)/g globin[a)]
Sampling time: not fixed[b)]

100 µg N-acetyl-S-(2-carbonamide ethyl)cysteine/g creatinine[a)]
Sampling time: end of exposure or end of shift

BLW (2011)

550 pmol N-(2-carbonamide ethyl)valine (AAVal)/g globin
Sampling time: not fixed[b)]

EKA (2011)

The following correlation between external and internal exposure is obtained:

Air	Erythrocyte fraction of whole blood
Acrylamide	N-(2-Carbonamide ethyl)valine (AAVal)
[mg/m³]	[pmol/g globin]
0.035	200
0.07	400
0.10	550
0.15	800
0.30	1600

Sampling time: not fixed[b)]

MAK value **not established**

Absorption through the skin (1985) H

Carcinogenicity (1985) Category 2

[a)] evaluated for non-smokers

[b)] changed to "sampling time: after exposure for at least 3 months" in 2016 (DFG 2016)

In 2007, the classification of acrylamide [79-06-1] in Carcinogen Category 2 and in Germ Cell Mutagen Category 2 was confirmed (translated in Greim 2009). A BAT value documentation has been available since 2000, in which due to the poor data at the time no exposure equivalents for carcinogenic substances (EKA) between the external and internal exposure to acrylamide could be derived. As parameter for internal acrylamide exposure, N-(2-carbonamide ethyl)valine (N-(2-carbamoyl ethyl)valine, AAVal), a haemoglobin (Hb) adduct of acrylamide, was under discussion (translated in Lewalter and Bolt 1999). In 2007, a biological guidance value (BLW) for the Hb adduct of acrylamide at the level of 15 µg N-(2-carbonamide ethyl)valine/l blood was established. The determination of the BLW was carried out under consideration of the avoidance of neurotoxic effects (translated in Angerer 2016). A threshold value for carcinogenic effects cannot be derived due to the genotoxic potential of acrylamide. To assess additional occupational exposure to acrylamide, therefore, biological reference values (BAR) as well as EKA are required. The present addendum is based on the data on background exposure improved since 2000 and the relationship between the biomarkers and inhalative exposure.

1 Selection of Indicators and Materials to be Investigated

The most widespread method for biomonitoring of acrylamide is the specific determination of the covalent adducts in haemoglobin. In this case, the modified Edman degradation procedure is used, a method established in specialiced laboratories on a worldwide basis (Bader et al. 2010; Bergmark 1997; Schettgen et al. 2002). By determining the Hb adducts, the mean exposure during the 120 days preceding sampling (lifetime of the erythrocytes) is recorded. It must be borne in mind that Hb adducts can be formed both by acrylamide itself as well as by the genotoxic metabolite glycidamide. The comprehensive database argues in favour of acrylamide Hb adducts as a parameter that can be used in assessment. The fact that exposure to genotoxic metabolites can be recorded using glycidamide argues in favour of this parameter. As further biological exposure parameters, the conjugates of acrylamide and glycidamide with glutathione can be used. As usual for glutathione conjugates, these are excreted with the urine in the form of mercapturic acids after cleavage of the glutaminic acid and glycine and acetylation of cysteine.

A study with oral administration indicates that the half-lives for the first phase in the renal excretion of N-acetyl-S-(2-carbonamide ethyl)cysteine (N-acetyl-S-(2-carbamoyl ethyl)cysteine, AAMA) and N-acetyl-S-(2-carbonamide-2-hydroxyethyl)cysteine (N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)cysteine, GAMA) are less than ten hours (first phase) immediately after the maximum of exposure (Boettcher et al. 2006). The exposure duration reflected by these parameters is thus clearly shorter than by the Hb adducts. In addition, these parameters require no long equilibration phase to attain a steady state, such as necessary to achieve the steady state concentration of an Hb adduct.

2 Exposure and Effects

A working group from the United Kingdom reports a study in which the blood levels of acrylamide Hb adduct AAVal of persons occupationally exposed to acrylamide were compared with individual exposures to acrylamide in the air (AA-air) (Jones et al. 2006). In this study, 60 employees (23 smokers, 37 non-smokers) engaged in the production of polyacrylamide were investigated. From nearly all participants, two blood samples were obtained at an interval of three months, and analysed for their AAVal level. During this period, between two and 13 personal air samples per person were taken over the entire workshift to assess the mean occupational inhalation exposure to acrylamide. In addition, to determine the exposure of the skin of the hands, cotton gloves were used as skin sample collectors during the times of the shift in which wearing protective gloves was not provided for. All 285 air samples obtained during the three months of the investigation were below the threshold limit value (workplace long term exposure limit) of 300 µg/m^3 valid in the United Kingdom. The maximum individual exposure was 282 µg/m^3. The mean value of all individual values was about 30 µg/m^3. The authors conclude that the acrylamide exposure of the workers was reasonably constant and that the personal airborne acrylamide levels correlated well with the mean AAVal levels at both time points of sampling (n = 50, r = 0.61). Mean personal airborne acrylamide levels and mean

acrylamide haemoglobin adduct levels were also well correlated (n = 46, r = 0.72). The correlation function was given as

$$C_{AAVal}[\text{pmol/g globin}] = 25.9 + 5.08 \times C_{AA\ air}[\mu g/m^3] \quad (1)$$

Application of this equation (1) yields the acrylamide adduct concentrations for selected air concentrations shown in Table 1.

Tab. 1 Correlations between acrylamide adducts and acrylamide in air according to equation (1)

Air Acrylamide	Erythrocyte fraction of whole blood N-(2-Carbonamide ethyl)valine (AAVal)	
[mg/m³]	[pmol/g globin]	[µg/l blood]
0.035	203.7	5.5
0.07	381.5	10.3
0.10	533.9	14.5
0.15	787.9	21.4
0.30	1549.9	42.0

3 Analytical Methods

To determine the haemoglobin adduct of acrylamide (AAVal) a method tested and published by the Commission is available (Bader et al. 2010) which has already been used in various studies (Bader et al. 2005; Kütting et al. 2009). From the erythrocyte haemolysate thus obtained, the protein fraction (globin) is precipitated using ethyl acetate, washed with organic solvents and finally dried. This globin is subsequently subjected to modified Edman degradation. Here, the alkylated N-terminal valine is cleaved from the protein chain and converted to the corresponding pentafluorophenyl thiohydantoin derivative. Using liquid-liquid extraction, the derivatives produced are extracted with diethyl ether from the protein matrix and separated from interfering substances by subsequent washing steps. Detection and quantification takes place after capillary gas chromatographic separation using mass spectrometry in the EI mode or NCI mode.

To determine the mercapturic acids of acrylamide and glycidamide, mainly procedures using LC-MS/MS technology are used (Boettcher and Angerer 2005; Schettgen et al. 2008). The Working Group "Analyses in Biological Material" has approved a reliable procedure for the determination of AAMA in urine (Schettgen et al. 2013).

4 Background Exposure

Apart from smoking, dietary intake represents the main exposure of the general population to acrylamide (Dybing et al. 2005; Smith et al. 2000).

4.1 Adducts

A series of studies is available in which the concentration of the acrylamide-Hb adduct in blood samples of the population was measured. In 1997, for the first time, it was described that AAVal can be found in practically all blood samples of the general population (Bergmark 1997). In eight not occupationally exposed non-smokers, the author found a mean AAVal concentration of 31 pmol/g globin. Non-exposed smokers, on the other hand, were found to have on average around fourfold higher AAVal concentrations (116 pmol/g globin, n = 10). In 18 non-exposed non-smokers, AAVal values between 20 and 70 pmol/g globin were found (Hagmar et al. 2001).

Data on the background exposure to acrylamide-Hb or glycidamide-Hb adducts are obtained on the basis of larger numbers of volunteers for France (Chevolleau et al. 2007), Norway (Bjellaas et al. 2007), Sweden (Hagmar et al. 2005) and Denmark (Olesen et al. 2008) (see Table 2). In addition, a multicentre study is available for 255 non-smokers and 255 smokers involving several European states (Vesper et al. 2008).

The medians for AAVal were, in these studies, between 31 pmol/g globin and 42.5 pmol/g globin for non-smokers. The medians for smokers are higher by a factor of 2 to 5 compared with non-smokers (see Table 2). In the French study (Chevolleau et al. 2007) and in the study involving several European states (Vesper et al. 2008), the mean values or medians for non-smokers were approximately equally as high for the glycidamide adduct (GAVal) as those for the acrylamide adduct AAVal. On the other hand, the GAVal concentrations in the Norwegian and Danish studies were only about half as high as the AAVal values.

Several studies are also available for the AAVal or GAVal levels of persons in Germany (see Table 2).

Tab. 2 Acrylamide- and glycidamide adduct concentrations (AAVal and GAVal) in the blood of persons not occupationally exposed to acrylamide

Country	Year	Group	n	AAVal	GAVal	References
				median/95th percentile (range) [pmol/g globin]		
Sweden	1991–1996	NS	70	31/– (20–100)	–	Hagmar et al. 2005
		S	72	152/– (30–430)	–	
France	2007	NS	52	27[a)]/– (9–70)	22[a)]/– (12–47)	Chevolleau et al. 2007
		S	16	53[a)]/– (16–163)	34[a)]/– (15–62)	
Norway	2006	NS	44	36.8/– (17.9–65.5)	18.2/– (6.7–45.6)	Bjellaas et al. 2007
		S	6	165.8/– (98.8–211)	83.2/– (29.1–99.0)	
Denmark	1993–1997	NS	235	35/88 (–)	21/53 (–)	Olesen et al. 2008
		S	139	122/277 (–)	60/126 (–)	
Europe	1992–2000	NS	255	42.5/88.3 (14.5–177)	39.9/83.3 (7.8–151)	Vesper et al. 2008
		S	255	121/285 (32.1–623)	92.8/198 (20.3–377)	
Germany	2000	NS	25	21/46 (< 12–50)	–	Schettgen et al. 2003
		S	47	85/159 (13–294)	–	
Germany	2004	NS	13	18/– (7–31)	18/– (9–23)	Schettgen et al. 2004
		S	16	83/– (25–199)	44/– (22–119)	
Germany	2005	NS	296	15/30 (< 11–44)[b)]	–	Bader et al. 2005
		S	99	44/140 (< 11–443)[b)]	–	
Germany	2002	NS	60	26.8/– (17.6–51.0)	–	Urban et al. 2006
		S	60	79.1/– (18.5–210.4)	–	
Germany	2003–2004	NS (incl. children)	91	30/51 (15–71)	34/52 (14–66)	Hartmann et al. 2008
Germany	2003–2004	NS	749	25.8/44.6 (3–68.1)	–	Kütting et al. 2009
		S	146	67.3/197.9 (8.2–331)	–	
Germany	2003–2004	NS (incl. children)	92	29.9/– (14.1–70.9)	35.2/– (13.8–65.8)	Schettgen et al. 2010

[a)] mean value

[b)] values calculated from µg/l blood (assuming a globin level of 144 g/l blood)

NS = non-smokers; S = smokers

In a study involving 72 persons from the German general population, AAVal concentrations between < 12 and 50 pmol/g globin (median: 21 pmol/g) were determined in non-smokers. Also in this collective, smokers were found to have approximately fourfold higher median AAVal concentrations in blood (Schettgen et al. 2003). In a further study 13 non-smokers and 16 smokers had very similar AAVal concentrations (Schettgen et al. 2004). The GAVal values for non-smokers also determined in these samples were approximately just as high as the AAVal values. The values for smokers indicate however that GAVal is formed at a lower ratio. In a more comprehensive study with the German general population (n = 395), the non-smokers (n = 296) were found to have a median AAVal level of 15 pmol/g globin (range < 11–44 pmol/g). For the smokers (n = 99), the corresponding mean value was, at 44 pmol/g globin (range: < 11–443 pmol/g), approximately threefold higher than the mean value for non-smokers. The AAVal levels of 60 non-smokers and 60 smokers were investigated in another study (Urban et al. 2006). Here, the non-smokers had a median AAVal concentration of 26.8 pmol/g globin (range: 17.6–51 pmol/g). Smokers showed approximately three times higher median AAVal values (79.1 pmol/g globin). The results of a study comprising 1008 persons (Kütting et al. 2009) revealed a median value of 25.8 pmol AAVal/g globin for adult non-smokers (n = 749). The smokers (n = 146) were found to have a median value of 67.3 pmol/g globin. The maximum values for non-smokers and smokers were 68.1 and 331 pmol AAVal/g, respectively. The publications by Hartmann et al. (2008) and Schettgen et al. (2010) present results for a subpopulation from the investigation reported by Kütting et al. (2009), in which an especially sensitive method using GC-MS/MS technology was applied. In 91 randomly selected non-smokers (including children), Hartmann et al. (2008) also investigated the GAVal concentrations in addition to the AAVal levels. As in the study by Schettgen et al. (2004), the GAVal values were approximately equally as high as the AAVal concentrations.

From the Hb adduct levels it is possible to calculate the daily acrylamide intake (Calleman 1996; Fennell et al. 2005). If one takes the data from the study by Kütting et al. (2009) as basis, the mean acrylamide intake of non-smokers is thus 0.41 µg/kg body weight and day, that of smokers 1.15 µg/kg body weight and day; maximum values are 1.36 and 4.83 µg/kg body weight and day, respectively. Passive smoking does not appear to significantly increase the acrylamide exposure of the non-smoking general population (Schettgen et al. 2010).

To summarise, it can be stated that, for the individual internal exposure of the general population to acrylamide in Germany, dietary intake and smoking habits are mainly responsible. In this context the individual smoking behaviour (number of cigarettes smoked per day) of the investigated persons must be thoroughly examined, in particular as regards “occasional” smoking. This is because, due to the long lifetime of erythrocytes, previous exposures are also recorded in the analysis.

4.2 Mercapturic acids in urine

There are also some studies available on the urinary excretion of the mercapturic acids of acrylamide and glycidamide in the general population (see Table 3). Bjellaas et al. (2005) investigated the excretion of AAMA and GAMA in the urine of five non-smokers and one smoker at different times of the day over a period of 48 hours, in this case starting with 24-hour fasting. Altogether, 65 urine samples from the non-smokers and 11 urine samples from the smoker were analysed. In the urine samples from the non-smokers, the median value was 29 µg AAMA/l or 61 µg AAMA/g creatinine and 17 µg GAMA/l or 29 µg GAMA/g creatinine. The median excretion in the smoker was 11 times higher for AAMA and six times higher for GAMA than in the non-smokers. Fasting for one day caused a 50% decrease in the concentration of metabolites. However, one day after the intake of a normal diet, the metabolite levels increased back to pre-fasting levels.

Boettcher et al. (2005) investigated the AAMA and GAMA excretion of 16 non-smokers and 13 smokers. For the non-smokers, the median was also determined to be 29 µg AAMA/l. The GAMA excretion of the non-smokers (median: 5 µg GAMA/l) was, however, clearly lower than in the investigation of Bjellaas et al. (2005). The median AAMA excretion in the smokers was determined to be 127 µg/l and thus approximately four times higher than in

the non-smokers. The median GAMA values of non-smokers and smokers revealed about the same ratio (median smokers 19 µg/l, non-smokers 5 µg/l).

Somewhat higher AAMA values were found by Urban et al. (2006) in the urine of 60 non-smokers (median: 41.6 µg/l). The median value for AAMA excretion in the urine of 60 smokers was 107.3 µg/l, and thus approximately three times higher than in the non-smokers. Also, the GAMA excretion of the non-smokers (median: 8.7 µg/l) was somewhat higher than in the Boettcher and Angerer (2005) study (median GAMA 5 µg/l).

The highest number of cases of non-smokers investigated for their AAMA and GAMA excretion is found in the study by Hartmann et al. (2008). The median AAMA excretion of 91 non-smokers aged 6 to 80 years was here 29 µg/l or 30 µg/g creatinine. In this investigation, the 95th percentile was given as 95 µg/l or 83 µg/g creatinine. The median GAMA excretion was 7 µg/l or 10 µg/g creatinine.

Schettgen et al. (2008) investigated the urinary AAMA excretion of 14 non-smokers and 14 smokers. The median value in the non-smokers was 52.6 µg/l urine. In the smokers, the median value was approximately four times higher (242.7 µg/l).

An investigation similar to that by Bjellaas et al. (2005), in which a small number of volunteers were repeatedly investigated, was carried out by Kopp et al. (2008) in six non-smokers. The median value for AAMA excretion in 54 urine samples was 24.0 µg/l. The median value for GAMA excretion was given as 3.82 µg/l.

Tab. 3 Urinary acrylamide and glycidamide mercapturic acid concentrations (AAMA and GAMA) of persons not occupationally exposed to acrylamide

Country	Year	Group	n	AAMA	GAMA	References
				median/95th percentile (range)		
Norway	2005	NS	5 (65)[a)]	29/– (10–178) µg/l	17/– (< 4–143) µg/l	Bjellaas et al. 2005[b)]
		S	1 (11)[a)]	337/– (64–500) µg/l	111/– (< 4–263) µg/l	
		NS	5 (65)[a)]	51/– (20.6–105) µg/g crea	25/– (< DL–97) µg/g crea	
		S	1 (11)[a)]	150/– (115–186) µg/g crea	40/– (< DL–106) µg/g crea	
Germany	2004	NS	16	29/– (3–83) µg/l	5/– (< 1–14) µg/l	Boettcher et al. 2005
		S	13	127/– (17–338) µg/l	19/– (3–45) µg/l	
Germany	2002	NS	60	41.6 µg/l/– (27.7–306.1 µg/24 h)	8.7 µg/l/– (5.3–71.3 µg/24 h)	Urban et al. 2006
		S	60	107.3 µg/l/– (25.3–538.9 µg/24 h)	15.0 µg/l/– (5.3–92.5 µg/24 h)	
		NS	60	43[c)]/– (16–180) µg/g crea[d)]	9[c)]/– (3–42) µg/g crea[d)]	
		S	60	109[c)]/– (15–317) µg/g crea[d)]	16[c)]/– (3–54) µg/g crea[d)]	
Germany	2003–2004	NS (incl. children)	91	29/95 (< 1.5–229) µg/l	7/32 (< 1.5–85) µg/l	Hartmann et al. 2008
		NS (incl. children)	91	30/83 (< DL–138) µg/g crea	10/28 (< DL–38) µg/g crea	
Germany	2007	NS	14	52.6/– (12.7–171) µg/l	–	Schettgen et al. 2008
		S	14	242.7/– (30.3–447) µg/l	–	
		NS	14	55.2/– (9.8–171) µg/g crea	–	
		S	14	178.7/– (35.1–401) µg/g crea	–	
Germany	2008	NS	6 (54)	24.0/– (7.8–79.8) µg/l	3.82/– (1.0–23.6) µg/l	Kopp et al. 2008

[a)] number of samples resulting from repeated investigations in brackets
[b)] study lasting 48 h including 24 h abstinence from food
[c)] mean value
[d)] values calculated on a creatinine excretion of 1.7 g/day; this includes the mean and range of value
crea = creatinine; DL = detection limit; NS = non-smokers; S = smokers

5 Evaluation

5.1 Evaluation of BAR

Owing to the strong effect of smoking habits on the acrylamide-haemoglobin adduct level and the mercapturic acid concentrations in the urine (see Section 4), these values can only be established for non-smokers. In addition, due to differences in nutrition in different countries, the BAR should be derived for the population living in Germany in particular.

To derive a BAR for the acrylamide adduct AAVal, mainly the data from three larger German studies (Bader et al. 2005; Kütting et al. 2009; Urban et al. 2006) are at present available. Of these, the study by Kütting et al. (2009) is prominent in that it involves the highest number of cases and presents separate data for the adult population. Here, a 95th percentile for adult non-smokers of 44.6 pmol/g globin was determined, on which the BAR for this parameter is based. Taking into account the uncertainties due to the influence of nutrition-based acrylamide intake, for acrylamide in **non-smoking** adults in the general German population

a BAR of 50 pmol N-(2-carbonamide ethyl)valine/g globin

is established.

Due to the long half-life of the adduct level, there is no fixed sampling time.

Note: The sampling time was changed to "after exposure for at least 3 months" in 2016 (DFG 2016).

All studies in which the reaction product of glycidamide, GAVal was determined in addition to AAVal, report approximately equally high concentrations in the blood of non-smokers for both reaction products. As, however, the database for the glycidamide adduct is much smaller than that for the acrylamide adduct, and the epoxidation rate can vary, a reference value for GAVal is not established due to these uncertainties.

Complementary to the Hb adduct of acrylamide, whose concentration level is obtained cumulatively from the exposures during the preceding three to four months, it seems useful to also establish a BAR for the excretion of the acrylamide mercapturic acid (AAMA). This is a biomarker representing daily exposure. Data on the urinary excretion of AAMA in occupationally non-exposed persons are available from the studies by Urban et al. (2006) and Hartmann et al. (2008), also for larger groups. In the publication by Urban et al. (2006), the results for the AAMA excretion are expressed in µg/24 hours. In addition, data on the 95th percentile are lacking. The data on AAMA excretion are given in the study by Hartmann et al. (2008) both volume-related (µg/l) and creatinine-related (µg/g creatinine). The study by Bjellaas et al. (2005), in which the excretion of AAMA and GAMA was monitored over 48 hours, shows that intraindividual variation in mercapturic acid concentrations is clearly reduced when related to creatinine. Also in the study by Hartmann et al. (2008), on a collective basis, a clearly smaller variation of the creatinine-related values was found. For this reason, the BAR for AAMA is determined as a creatinine-related value.

In the study by Hartmann et al. (2008), the 95th percentile for 91 non-smokers was 83 µg AAMA/g creatinine. However, 23 of the investigated volunteers were children and five were over 65 years old. Recalculation of the original data which included only the adult persons aged 18–65 years (n = 63) resulted in a 95th percentile for AAMA excretion of 85 µg/g creatinine (Hartmann 2011).

Taking into consideration that the AAMA values in the study by Urban et al. (2006) as recalculated under assumption of a mean creatinine excretion of 1.7 g/day are somewhat higher than the values published in the study by Hartmann et al. (2008),

a BAR of 100 µg N-acetyl-S-(2-carbonamide ethyl)cysteine/g creatinine

is established for acrylamide in **non-smoking** adults in the general German population.

In this case, sampling has to be carried out at the end of exposure or end of shift.

5.2 Evaluation of EKA

The study by Jones et al. (2006) has provided a well-documented relationship between exposure to acrylamide in the air and the concentration of the acrylamide adduct N-(2-carbonamide ethyl)valine. This can be used without limitations in establishing the exposure equivalents.

Using the equation given by Jones et al. (2006) the following **EKA** are obtained:

Air **Acrylamide** **[mg/m³]**	**Erythrocyte fraction of whole blood** **N-(2-Carbonamide ethyl)valine (AAVal)** **[pmol/g globin]**
0.035	200
0.07	400
0.10	550
0.15	800
0.30	1600

There is no fixed sampling time.

Note: The sampling time was changed to "after exposure for at least 3 months" in 2016 (DFG 2016).

5.3 Re-evaluation of the BLW

Since establishment of the BLW for acrylamide in 2007, no new data have been published which would justify a change in the BLW of 15 µg N-(2-carbonamide ethyl)valine/l blood. As a result of the adaptation of the concentrations given for adducts at the N-terminal valine of globin, the BLW unit µg/l blood has been converted into pmol/g globin. Using an average globin level of 144 g/l blood and the molar mass of 188.2 g/mol for N-(2-carbonamide ethyl)valine, the BLW for acrylamide is converted and established at

550 pmol N-(2-carbonamide ethyl)valine/g globin.

There is no fixed sampling time.

Note: The sampling time was changed to "after exposure for at least 3 months" in 2016 (DFG 2016).

6 Interpretation of Results

In interpreting the results, personal influencing factors in particular, such as for example the accurate anamnesis of smoking habits, are to be taken into account. For persons reporting "smoker" in their patient histories, in the German studies, the median values for AAVal were in the range of 44–85 pmol/g globin. The 95th percentiles of the AAVal concentration varied within a range of 140–198 pmol/g globin. The consequently recognisable increase in acrylamide exposure from smoking by a factor of 3 to 4 is quite plausible, if one compares the estimated dietary intake of acrylamide of between 0.2 to 1.4 µg/kg body weight and day (Dybing et al. 2005) with the estimated daily acrylamide exposure from smoking of 3 µg/kg body weight and day (Bergmark et al. 1997).

The possible indicators for an acrylamide biomonitoring presented in Section 1 constitute a useful instrument in assessment exposure. For assessment, beside the BAR, also the adduct levels can be used which are obtained from the EKA using the acceptable risk of 0.07 mg/m³ for acrylamide published in the Technical Rules for Hazardous Substances 910 of the Committee for Hazardous Substances (AGS 2014).

The BAR relates to urine at a normal concentration, in which the creatinine concentration should be within the range of 0.3–3 g/l. In addition, the Commission considers selecting a more restricted target range of 0.5–2.5 g/l for urine samples to be useful, as this further improves the validity of the analyses undertaken. As a rule, in urine samples outside the limits cited above, a repetition of the analysis 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.

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