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Acrylamide in children – exposure assessment via urinary acrylamide metabolites as biomarkers

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Abstract

Acrylamide (AA), a substance classified as probably carcinogenic to humans, was detected for the first time in food products in 2002. AA can be primarily found in foods containing carbohydrates and proteins, where it is formed during the heating process. Exposure assessment based on food consumption data revealed an average daily intake of AA between 0.3 and 0.8 μg/kg BW/day. These data have been confirmed by human biomonitoring using haemoglobin adducts of AA in blood or the specific mercapturic acids in urine. However, human biomonitoring data on the internal exposure of children were only sporadically available. Especially data about the excretion of both relevant mercapturic acids were missing. The mercapturic acids other than the haemoglobin adducts give the recent AA exposure of the last 24 h. In this study, we quantify the internal exposure of AA and the genotoxic metabolite glycidamide (GA) in 110 children with regard to their exposure through diet and/or environmental tobacco smoke.

Material and methods: Hundred and ten 5–6-year-old children were randomly selected. Their dietary habits as well as their exposure to the environmental tobacco smoke were assessed by means of a questionnaire. By means of spot urine samples, mercapturic acids of acrylamide (AAMA) and mercapturic acids of glycidamide (GAMA) were analysed with LC-ESI-MS/MS.

Results: Median (95th percentile) urinary levels were 36.0 (152.7) μg AAMA/l and 13.4 (55.9) μg GAMA/l. Based on the metabolite levels, the median uptake of acrylamide was calculated to be 0.54 μg/kg BW/d. A number of associations with the consumption of French fries, various potato products, as well as fried cereals could be found. Significant results were found for French fries. No correlations between the exposure to environmental smoke and cotinine levels in urine were found.

Conclusion: This is the first study to show the presence of AAMA and GAMA in urine specimens of 110 children, thus providing evidence for a background exposure by nutrition. Median (95th percentile) uptake of AA in children was 0.54 (1.91) μg/kg bodyweight and day, exceeding exposure in adults by 50%. These findings support the efforts to minimize AA formation and contamination in food. Comparing our findings with that of other human studies, there

Abbreviations: AA, acrylamide; GA, glycidamide; AAMA, *N*-acetyl-*S*-(2-carbamoylethyl)cysteine; GAMA, *N*-acetyl-S-(2-carbamoyl-2hydroxyethyl)cysteine.

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are hints that children have a higher AA intake than adults and that children more effectively oxidize AA. Both findings indicate that children might be the most vulnerable group of the population.

Keywords: Acrylamide; Children; Internal exposure; Human biomonitoring; Diet

Acrylamide (AA) gained great public and scientific interest when the WHO in 2002 published concentrations of AA in lot of foods (WHO, 2002). Especially in foods containing carbohydrates and proteins, AA is formed during the heating process through interaction of amino acids, especially asparagine, with reducing sugars like glucose (Mottram et al., 2002; Stadler et al., 2002; Tareke et al., 2002). On account of this, many food products have been tested for this substance. As a matter of fact, AA was found in fried potatoes, French fries, chips, as well as in biscuits, fried cereals, coffee, etc., with peak concentrations reaching several mg/kg (BfR, 2002, 2004; Dybing et al., 2005; JECFA, 2005; JIFSAN, 2004).

Exposure assessment based on food consumption data demonstrated the average daily intake of AA between 0.3 and 0.8 μg/kg BW/d not only in Germany, but in other European countries as well (WHO, 2002; Konings et al., 2003; Mosbach-Schulz et al., 2003; Madle et al., 2003; Svensson et al., 2003). Infants and especially young people were found to be even more exposed to AA through their diet because of their lower body weight and increased consumption of fast food and snacks (Konings et al., 2003; Mosbach-Schulz et al., 2003).

Human biomonitoring gives the means to determine the amount of substance which is really incorporated. No further assumptions as to exposure have to be made. In 1993, a method for analysing haemoglobin adducts of AA and its oxidation product glycidamide (GA) in workers exposed to AA was published for the first time (Bergmark et al., 1993). Meanwhile, many human biomonitoring studies of general populations have been published using these parameters. As a result, haemoglobin adducts of AA and GA are to be found in the general population, with significantly higher levels in smokers (between 2 and 4 times higher) than in non-smokers (Schettgen et al., 2003, 2004; Bader et al., 2005; Hagmar et al., 2005; Urban et al., 2006; Wirfält et al., 2007; Bjellaas et al., 2007a). In Germany, the Commission on Human Biomonitoring has published a reference value for AA-haemoglobin in the population (HBM Kommission, 2008).

Additionally, in 2005, a method for analysing mercapturic acids of acrylamide (AAMA) and glycidamide (GAMA) metabolites in urine was established (Boettcher and Angerer, 2005). Using this method, once again several times higher levels of specific urinary metabolites were found in smokers compared to non-smokers (Boettcher et al., 2005; Bjellaas et al., 2005, 2007b). Moreover, it could be shown that on consuming foods containing AA, such as French fries, the levels of AAMA and GAMA increased 10-fold, whereas after several days of following an AA-free diet, the levels decreased to $\frac{1}{10}$ of the original level (Boettcher et al., 2004). In another study, 48 h fasting resulted in a >90% reduction of the AA metabolite levels in urine (Boettcher et al., 2006).

Apart from food and smoking, there might be detectable exposure via cosmetic products, though in the European Union AA has been limited to 0.1 ppm for leave on cosmetic products and 0.5 ppm for other cosmetic products (EU, 1999; NN, 2005). To date, no data are available on internal AA exposure via cosmetic products or environmental tobacco smoke.

Though exposure to AA in children is supposed to be higher than in adults – based on modelling food consumption data – only sporadic human biomonitoring data on internal exposure of children are available yet. Therefore, a group of children was tested for their internal exposure to AA by analysing urinary levels of AAMA and GAMA.

Methods

In connection with the routine medical tests conducted before starting school, children and their families were asked for their voluntary participation in this study. The collective study comprised a random sample of 110 children, asked consecutively during the medical examinations of the school beginners, 63 boys and 47 girls, aged 5–6 years. All but two of the families contacted agreed in participation. The parents of the children were asked to fill in a questionnaire on dietary habits as well as on environmental tobacco smoke in their homes. A spot urine sample was collected from the children during their visits, i.e. from 8 a.m. to 1 p.m.

The urine specimen was immediately frozen at −18 °C until analysis. The analytical method applied to quantify AAMA and GAMA in the urine samples is described elsewhere (Boettcher and Angerer, 2005). In short, for 4 ml of each urine sample, isotope labelled internal standard solutions (d_3-AAMA, d_3-GAMA) were added. The analytes were extracted at an ENV+ (Isolute IST) SPE cartridge prior to ESI-RP-LC-MS/MS analysis (Sciex API 2000) in the negative isonization mode. Each

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series included calibration standards that were prepared by diluting aqueous working solutions of AAMA and GAMA with urine in the concentration range from 10 to 500 µg/l. Linear calibration curves were obtained by plotting the quotients of the peak areas of AAMA and GAMA and the corresponding d3-labelled standards as a function of the concentrations used. The correlation coefficients were all higher than $r = 0.99$ for both AAMA and GAMA. Detection limits for both analytes were 2 µg/l urine. For quality control purposes, spiked urine samples were included in each analytical series. The between-series precision for AAMA and GAMA was found to be 7% and 10% ($n = 6$) for the lower concentration (Q_{low} 20 µg/l) and 6% and 5% for the higher concentration (Q_{high} 100 µg/l), respectively.

Calculation of the exposure based on the metabolite levels was done using two estimation models based upon the volume and the creatinine-related urinary molar metabolite concentrations:

Creatinine-relation calculation:

$$\frac{\text{AAMA} + \text{GAMA}(\mu\text{mol/Creatinine}) * \text{CE}_{\text{smoothed}} * \text{MW}_{\text{AA}}}{F_{\text{UE}} * \text{kg BW}}$$

Volume-based calculation:

$$\frac{\text{AAMA} + \text{GAMA}(\mu\text{g/l}) * \text{Urine(l/day)} * \text{MW}_{\text{AA}}}{F_{\text{UE}} * \text{kg BW} * \text{MW}_{\text{Metabolite}}}$$

The molecular weights are as follows: AA 71, AAMA 230, GAMA 246. The smoothed creatinine excretion rates $\text{CE}_{\text{smoothed}}$ are body height- and gender-based reference values for urinary creatinine excretion for healthy white children (Remer et al., 2002). The molar fraction F_{UE} describes the molar ratio between the urinary excreted amount in the form of the two metabolites and the amount of AA taken up; this ratio is set at 50% according to Boettcher et al. (2006). Kg BW is set for body weight in kg. In the volume-based calculation, reference value for the mean excreted urine volume (Urine l/day) is used, according to Tabella Geigy: adults 1.4 l/day, children 0.4 l/day (Ciba-Geigy, 1977).

Cotinine levels were determined as published in the method collection of Analyses of Hazardous Substances in Biological Materials by the Deutsche Forschungsgemeinschaft (German Research Foundation) (DFG, 2003). For 2 ml urine, d_3-labelled internal standard (d_3-cotinine) was added. After alkalization with 5 M sodium hydroxid solution, cotinine was extracted via liquid–liquid extraction using dichloromethane. The organic phase was evaporated to dryness, the residue was dissolved in 1 ml Toluol and 1 µl of the solution was injected into the GC–MS system. Calibration was carried out in urine, between 2 and 220 µg/l. The correlation coefficients of the resulting graphs were all higher than $r = 0.99$. The detection limit was 0.2 µg/l urine. Each analytical run included a quality control (QC) sample (10 µg/l) and reagent blank to assure the accuracy and reliability of the data. The between-series precision was 4% ($n = 11$).

Statistical analyses were done using the SPSS programme Version 11, nonparametric tests Mann–Whitney *U*-test and two-tailed Spearman Rank correlation tests.

Results

Urinary levels of AAMA and GAMA/l and a creatinine basis are shown in Table 1. Median levels were 36.0 µg AAMA/l and 13.4 µg GAMA/l, the 95th percentiles were 152.7 µg AAMA/l and 55.9 µg GAMA/l. A strong correlation between AAMA and GAMA was observed (r: 0.668; $p > 0.001$). The ratio GAMA/AAMA was 0.42 ± 0.17 (0.06–1.2). With increasing urinary AAMA levels, the GAMA/AAMA ratio decreased (r: −0.43; $p > 0.001$). GAMA/AAMA ratio was 0.32 ± 0.14 in children with AAMA levels in the upper quartile and 0.48 ± 0.20 in children with AAMA levels in the lower quartile.

Children who regularly consumed French fries, chips and other fried potato products, as well as other fried foods and biscuits, had higher urinary levels of AA metabolites in their urine. This difference, however, was significant only for French fries (Table 2).

An impact of passive smoking could not be seen. Children who are exposed to environmental tobacco smoke at home did not exhibit higher levels of AA

Table 1. Urinary levels of acrylamide metabolites AAMA and GAMA/l and on creatinine basis

	>LOD	Mean ± sdev	Maximun	*P* 50	*P* 95
Liter basis					
AAMA (µg/l)	109	57.8 ± 119.5	1225.3	36.0	152.7
GAMA (µg/l)	106	18.3 ± 15.3	90.1	13.4	55.9
AAMA + GAMA (µg/l)	109	76.1 ± 130.2	1315.4	49.9	199.9
Creatinine basis					
AAMA (µg/g) crea	109	76.7 ± 98.7	1012.7	59.3	158.7
GAMA (µg/g) crea	106	25.8 ± 13.9	77.9	22.4	57.8
AAMA + GAMA (µg/g) crea	109	102.5 ± 107.6	1087.1	82.3	205.3

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Table 2. Dietary habits of the children and median urinary levels of AAMA and GAMA

	⩽1x/month	⩽2x/week	⩾3x/week	>3x/Week versus <1x/month	Two-tailed Spearman Rank correlation tests	
	Median (μg/l)				*R*	*p*
AAMA						
Potato chips	29.98	49.57	40.47	0.518	**0.192**	**0.044**
Crackers, Popcorn	27.96	39.94	34.61	0.853	0.030	0.753
Biscuits, Nuremberg ginger bread	32.01	39.74	56.5	0.273	0.092	0.341
French fries	25.91	42.50	57.85	**0.003**	**0.322**	**0.001**
Fried food (calamares)	30.88	40.37	56.5	**0.037**	0.154	0.108
Crispbread	34.86	38.08	33.31	0.965	−0.029	0.763
Toasted bread	32.01	39.88	34.49	0.742	−0.015	0.874
Muesli, cereals	24.87	33.19	38.01	0.091	0.122	0.245
GAMA						
Potato chips	13.04	14.83	14.51	0.573	0.115	0.232
Crackers, Popcorn	13.55	13.7	12.86	0.883	−0.015	0.876
Biscuits Nuremberg ginger bread	13.24	13.17	26.41	0.131	0.065	0.497
French fries	11.18	14.56	30.77	**0.004**	**0.310**	**0.001**
Fried food (calamares)	13.04	14.19	23.04	**0.022**	0.133	0.165
Crispbread	13.25	15.28	12.52	0.785	−0.008	0.937
Toasted bread	12.32	17.85	13.16	0.59	−0.015	0.875
Muesli, cereals	11.49	16.11	13.25	0.352	0.016	0.869

Table 3. Exposure to environmental tobacco smoke and median urinary levels of AAMA and GAMA

	At least one familiy member smoking		Smoking in the flat		Mann–Whitney *U*-test *p*
	Yes	No	Yes	No	
AAMA (μg/l)	37.1	34.9	37.6	24.6	0.265
GAMA (μg/l)	13.5	13.2	13.8	11.9	0.393
AAMA + GAMA (μg/l)	52.1	47.7	52.7	35.8	0.393

metabolites in urine. This was affirmed by the fact that there was no correlation between AA metabolite levels and cotinine levels in urine (Table 3, Fig. 1).

Moreover, we found no associations between urinary AA metabolite levels and the use of cosmetics such as cream, shampoo, body lotion.

Based on the urinary metabolite levels detected, the intake of AA was calculated (see Methods) using two estimation models based upon the volume and the creatinine-related urinary metabolite concentrations. Median AA exposure was 0.54 μg/kg BW (volume-based) and 0.88 μg/kg BW (creatinine-based), P 95 were 1.91 and 2.27 μg/kg BW, respectively (Table 4).

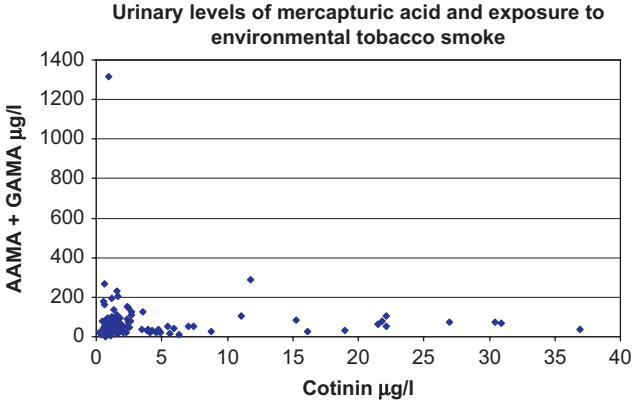

Fig. 1. Urinary levels of AAMA + GAMA and exposure to environmental tobacco smoke assessed via cotinine levels in urine.

Discussion

The detection of AA in food raised great concern because various national and international organizations have classified AA to be probably carcinogenic to humans (DFG, 2006; US-EPA, 1994; EU, 2001; IARC, 1994). This classification was based on animal experiments where a variety of cancer locations were observed in different rodent species.

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Table 4. Acrylamide intake of the children calculated using two estimation models – μg/kg BW/day

Method	$x \pm$ sdev	Max	*P* 50	*P* 95
Creatinine excretion based (Remer et al. 2002)	1.13 ± 1.17	11.6	0.88	2.27
Volume based (Ciba-Geigy, 1977)	0.81 ± 1.63	17.0	0.54	1.91

Acrylamide is readily absorbed and metabolized in the body. It is in part directly bound to nucleophilic molecules and sites like haemoglobin and glutathione. Another part is oxidized by cytochrome P4502E1 (Cyp2E1) to form GA the epoxide of AA. GA, is thought to be the ultimate genotoxic agent of AA (Paulsson et al., 2003). Marked species differences in the metabolism of AA were found with ratios of GAMA/AAMA 0.23 in rats and 0.52 for mice. The higher-rate GAMA/AAMA in mice compared to rats is in accordance with the observation that mice are much more susceptible to AA than rats. This is due to a higher enzymatic CYP2E1 activity and thus oxidative metabolism of AA to GA, the predominant carcinogen (Twaddle et al., 2004; Barber et al., 2001; Sumner et al., 2003).

We present for the first time human biomonitoring data on internal exposure of 110 children to AA and its genotoxic metabolite GA. The analytical method (Boettcher and Angerer, 2005) for the determination of the mercapturic acids AAMA and GAMA has proven to be sensitive and convenient for analysing background exposures in children. In all children with one exception, exposure exceeded the limit of detection. Median values of AAMA and GAMA were 36 and 13 μg/l. The *P* 95 values were 153 and 56 μg/l. Compared to published data, the median AAMA levels are similar to median levels analysed in studies on non-smoking adults. Reported median levels of Boettcher et al. (2005), Urban et al. (2006) and Bjellaas et al. (2007a, b) were 29, 42 and 32 μg/l, respectively. However, the excretion of the oxidative urinary metabolite, the GAMA, seems to be enhanced in the children population. The median level of 13 μg/l is higher than the median GAMA levels reported in the other studies of 5, 9 and 3 μg/l (Boettcher et al., 2005; Urban et al., 2006; Bjellaas et al., 2007a, b).

The ratio GAMA/AAMA was 0.4 (0.06–1.2) and was thus higher than in the study of Boettcher et al. (2005), where a median ratio of 0.22 (0.10–0.53) was found in adult non-smokers and a ratio of 0.15 (0.03–0.30) in smokers (Boettcher et al., 2005). This difference may indicate a more potent oxidative metabolism in children.

With increasing urinary AAMA levels, the GAMA/AAMA ratio decreased in the children (r: −0.43; $p > 0.001$). This observation is in accordance with the results of Sumner et al. (2003) and Bergmark et al. (1991) and the dose-dependent conversion of AA to GA in rats with increasing conversion to GA up to 50% at lower doses (<5 mg/kg BW) (Bjellaas et al., 2005). Moreover, this is also in accordance with the observation in smokers and non-smokers where AA exposure in smokers always exceeded that of non-smokers, several fold, and where GAMA/AAMA was always lower than in non-smokers (Bjellaas et al., 2005).

Human studies in toxicokinetics have estimated that about 50% of the AA taken up is excreted via the mercapturic acids within 24 h (Boettcher et al., 2006; Fuhr et al., 2006). Thus, it was possible to calculate the uptake of AA from the levels of urinary metabolites. In the volume-based model, median AA intake was 0.54 μg/kg BW/day. In the creatinine-based model it was 0.88 μg/kg BW/day. The differences in the 95th percentile were lower: 1.91 μg/kg BW/day in the volume-based model vs. 2.27 μg/kg BW/day in the creatinine-based model. Comparable differences in the results based upon the different methods had been shown recently when these methods were applied in the calculation of exposure to phthalates (Wittassek et al., 2007). At the present, neither of the methods can be preferred over the other one, and according to Wittassek et al. (2007), both methods have to be regarded as equiprobable. As a result, AA intake in children (0.88 μg/kg BW/day in the creatinine-based method) was about 1.5 times higher than in adults (0.50 μg/kg BW/day (Hartmann et al., in preparation).

In accordance with the exposure calculations by modelling AA levels in foods and consumption data, the effect of diet – especially the consumption of fried potato products and fried cereals – could be confirmed by our study. Children, who reported to consume fried potatoes, chips or fried cereals regularly, exhibited significantly higher metabolite levels in their urine specimen than those who consumed these food items less frequently. An impact of passive smoking could not be seen, however; obviously, exposure to AA via environmental tobacco smoke is too low to result in a measurable increment of urinary levels of AAMA or GAMA.

In our study, we used a questionnaire modified from that used by Kütting et al. (2005). Kütting et al. (2005) had studied the effect of diet on the internal exposure assessed by haemoglobin adduct levels of AA as biomarkers. They could not find any association between the internal exposure and the diet reported.

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Amongst others this is due to the fact that haemoglobin adduct levels represent the exposure for up to 3 months, whereas most of the study participants are not able to exactly remember their diet for such a long time. AA-metabolites in urine, however, represent the short-term dietary exposure to AA and it is obvious that short-term dietary exposure can be remembered much better than long-term exposure. Thus, it is plausible that in our study good and significant associations could be found in accordance with exposure calculations.

Conclusion

These findings are in concordance with the exposure assessment by modelling dietary intake. They prove an internal exposure of all children in our society. Because AA is classified as probably carcinogenic in humans, our data of ubiquitous exposure to AA in children support the efforts to minimize AA contents in food.

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