

Addendum to Acrylamide

BLW (2007)

15 µg N-(2-carbonamideethyl)valine/l blood*

sampling time: not fixed

MAK value

Not established

Absorption through the skin (1985)

H

Sensitization (2006)

Sh

Carcinogenicity (1985)

Carcinogen Category 2

* No longer valid. For updated values/classifications please refer to <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

The classification of acrylamide in carcinogen category 2 and in germ cell mutagen category 2 was confirmed in 2007 (Greim 2007, translated).

The substance was evaluated in 1996 and no exposure equivalents for carcinogenic substances (EKA) between external and internal exposure to acrylamide could be derived due to the insufficient data at the time. N-(2-carbonamideethyl)valine (N-(2-carbamoyl)ethyl)valine, AAV_{al}), a haemoglobin adduct of acrylamide, is being discussed as parameter for internal exposure to acrylamide (see Documentation 1996, translated).

In 2002 the Swedish National Food Agency published the results from acrylamide content measurements in various foods. They thus confirmed the hypothesis that acrylamide is produced by heating foods containing carbohydrates and other proteins (Tareke et al. 2002). Thereby, not inconsiderable quantities of the haemoglobin adduct of acrylamide were found in the blood of control persons, for which initially there was no explanation. Since then, the media have been paying increased attention to the food-related exposure of the general population to acrylamide, as acrylamide was found to be clearly carcinogenic in animal studies.

In the following, no detailed presentation of the toxicology of acrylamide in humans and animals is given, and there is no description of the large number of animal studies investigating the carcinogenicity and the in vitro genotoxicity of acrylamide. In this context special reference is made to the MAK documentation (Greim 2007, translated). For derivation of a "Biologischer Leitwert" (BLW), the neurotoxicity of acrylamide is at the focus of this documentation. The nervous system shows a highly sensitive reaction to acrylamide.

1 Metabolism and Toxicokinetics

1.1 Absorption and distribution

At the workplace, acrylamide is taken up by inhalation, dermally and orally. It is completely absorbed and rapidly distributed throughout the entire body as a result of its solubility in water (Miller 1982). After administration of acrylamide-containing potato chips to 6 individuals (average age 26.6 years) $60.3\% \pm 11.2\%$ of the ingested acrylamide was excreted in the urine after 72 hours in the form of acrylamide and its mercapturic acids, N-acetyl-S-(2-carbonamideethyl)cysteine (AAMA) and N-acetyl-S-(2-carbonamide-2-hydroxyethyl)cysteine (GAMA). With an average of 4.4%, the acrylamide excreted in unchanged form plays a minor role. With 50% AAMA represents the major part of the metabolites excreted in the urine. The half-lives are 2.4 hours (acrylamide), 17.4 hours (AAMA) and 25.1 hours (GAMA) (Fuhr et al. 2006).

After oral administration of 0.99 mg deuterium-labelled acrylamide to one individual, 57% of the ingested acrylamide dose was excreted in the form of both mercapturic acids in the urine within 46 hours (Böttcher et al. 2004 b). The two deuterized mercapturic acids were still detectable in the urine after 46 hours. Whereas the elimination maximum of AAMA was already attained after 11.5 hours, this was 22.5 hours in the case of GAMA.

Water-soluble acrylamide enters the breast milk (Sörgel et al. 2002) and passes the placental barrier. In 11 mother-child pairs, it was found that the acrylamide/haemoglobin adduct level in the blood of mothers closely correlates with that in the umbilical blood. Although the concentration of AA adducts in the two matrices is at a ratio of 2:1, it must be assumed that the relative internal acrylamide dose (mg/kg body weight) in neonates is at least equal to that of the mother. The shorter life span of neonatal erythrocytes, which results in a comparably low level of N-(2-carbonamideethyl)valine (AAVal) argues in favour of this (Schettgen et al. 2004 a).

1.2 Metabolism

From animal studies, it is known that part of the absorbed acrylamide is oxidized to glycidamide by the cytochrome P-450 enzyme 2E1 (Sumner et al. 1999). Both acrylamide and glycidamide bind to nucleophilic sites of macromolecules in the body. These are especially sulfhydryl or amino groups. Glycidamide has greater electrophilic and reactive properties than acrylamide, and is held responsible for the mutagenic and carcinogenic effects of acrylamide (Besaratina and Pfeifer 2004).

In the phase II metabolism, acrylamide as well as glycidamide are bound to glutathione and finally excreted in the urine in the form of the mercapturic acids AAMA and GAMA. Quantitatively, the formation of AAMA, the reductive metabolite, is in this case of greater importance than that of the mercapturic acid of

GAMA with its more pronounced genotoxic and carcinogenic properties (Sumner et al. 1997). The ratio between the two mercapturic acids AAMA and GAMA plays a decisive role. In rats, this ratio is 5:1, in mice 2:1 (Sumner et al. 1992). These results support the observation that mice react to the carcinogenic effects of acrylamide with greater sensitivity than rats (Paulsson et al. 2001, 2002; see Section 2.2).

Whereas a series of animal studies investigating the metabolism of acrylamide are available, its metabolism in humans was not investigated until recent years. In the study already mentioned, in which deuterium-labelled acrylamide was administered orally, 52% of the dose was eliminated in the form of AAMA and 5% in the form of GAMA within 46 hours after administration. This means that the ratio between the less and the more pronounced genotoxic metabolic pathway in humans is about 10:1 (Böttcher et al. 2006 b). A similar ratio between AAMA and GAMA was observed after administration of potato chips containing acrylamide (Fuhr et al. 2006). Here, an average 50% of the acrylamide dose in the form of AAMA and 5.9% in the form of GAMA were excreted in the urine within 42 hours after administration. In addition, this Working Group also found still unchanged acrylamide in the urine, though this accounted for only 4.4% of the dose.

In the general population, the ratio between the two mercapturic acids is found to be different than after single acrylamide administration. The ratio between the reductive and the oxidative metabolism pathway (AAMA:GAMA) is here present at an average of 6:1 (Böttcher et al. 2005).

1,2-dihydroxypropionamide, a further metabolite of acrylamide, has since then been identified in human urine, which is produced by the hydrolysis of glycidamide (Fennal and Friedman 2005). Figure 1 shows the human metabolism of acrylamide in simplified form. The reaction product of acrylamide with the terminal valine of haemoglobin (N-(2-carbonamideethyl)valine, AAVal) was demonstrated in members of the general population for the first time in 1997 (Bergmark 1997). These acrylamide-Hb levels were surprisingly high (31 pmol AAVal/g globin, non-smokers); three times higher adduct levels were measured on average in tobacco smokers (116 pmol AAVal/g globin). With the use of highly selective analytical methods it could be demonstrated that haemoglobin adducts of the ultimate carcinogen glycidamide also occur in the blood of the general population. In non-smokers, the ratio of N-(R,S)-(2-carbonamide-2-hydroxyethyl)valine (GAVal) to AAVal was 0.96 on average (maximum value: 1.7) (Paulsson et al. 2003; Schettgen et al. 2004 b). The ratio between Hb adducts GAVal and AAVal is thus around five times higher than that between the corresponding mercapturic acids of glycidamide and acrylamide. This indicates a higher reactivity of glycidamide in humans than expressed by the elimination of the two mercapturic acids (Böttcher et al. 2006 b).

In smokers, who absorb considerably more acrylamide than non-smokers, the GAVal to AAVal ratio was 0.7. This could mean that the importance of the oxidative metabolism decreases with increasing acrylamide exposure in humans.

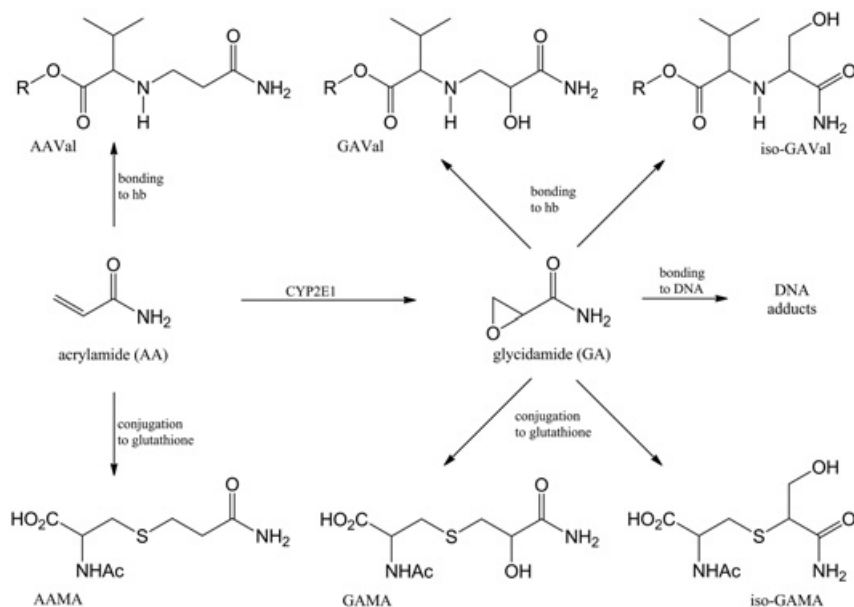


Figure 1 Simplified metabolism of acrylamide in humans

AA = acrylamide; GA = glycidamide

AAMA = N-acetyl-S-(2-carbonamideethyl)cysteine

GAMA = N-acetyl-S-(2-carbonamide-2-hydroxyethyl)cysteine

AAVal = N-(2-carbonamideethyl)valine; GAVal = N-(2-carbonamide-2-hydroxyethyl)valine

CYP2E1 = cytochrome P-450 enzyme 2E1

Both acrylamide and glycidamide form haemoglobin adducts in vivo, whereas DNA adducts are exclusively formed by glycidamide in vivo (IARC 1994; JIFSAN 2002).

In humans, no DNA adducts of acrylamide or glycidamide could be detected up to now.

After administration of acrylamide to rats and mice, N-7-(2-carbonamide-2-hydroxyethyl)guanine, a DNA adduct of glycidamide, could be found in the various organs of both species in very similar concentrations. This indicates that glycidamide is equally distributed in the body and that only glycidamide shows a mutagenic and carcinogenic potential (Segerbäck et al. 1995). Furthermore, in 2003, a further DNA adduct of glycidamide, N-3-(2-carbonamide-2-hydroxyethyl)adenine, could be identified. It is only present, however, in a quantity a hundred times lower than that of N-7-(2-carbonamide-2-hydroxyethyl)guanine after acrylamide administration (Da Costa et al. 2003). In mice, an increase in DNA adduct concentration in the liver was already found 8 hours after administration of 50 mg acrylamide/kg body weight by gavage (Doerge et al. 2005; Twaddle et al. 2004). This

corresponds to approximately one hundred times the estimated mean acrylamide absorption by non-smokers.

2 Critical Toxicity

2.1 Neurotoxicity

The central and the peripheral nervous system are targets after chronic exposure to acrylamide (WHO 1985). In the central nervous system, ataxia, tremor, reflex disturbances, incoherent speech and conditions of confusedness were observed (Hashimoto 1980). Disturbances of the peripheral nervous system manifested themselves through sensations of numbness in hands and feet, loss of foot reflexes, muscular atrophy and ataxia (EPA 1993). These neurotoxic effects of acrylamide were found to be reversible in a large number of cases (Auld and Bedwal 1967; Davenport et al. 1976; Igisu et al. 1975). In Swedish tunnel workers exposed by inhalation to a mixture containing acrylamide, reversible peripheral nerve disturbances were identified. In this case, the acrylamide-Hb level correlated with the neurological symptoms (Hagmar et al. 2001). Significantly more frequent neurotoxic symptoms were found in 41 Chinese workers exposed to a mixture of acrylamide and acrylonitrile than in a control group. Here too, the neurotoxic effects correlated with the internal acrylamide exposure, which was identified in the form of acrylamide-mercapturic acid excretion in urine and the acrylamide-Hb adduct level in blood (Calleman et al. 1994).

The literature discusses different mechanisms for the neurotoxic effects of acrylamide. More recently, this discussion has become concentrated on two competing hypotheses, i.e. inhibition of the kinesin-based rapid axonal transport (Sickles et al. 2002) and direct inhibition of neurotransmission (LoPachin 2002).

In every case, however, binding of the electrophilic toxic substances acrylamide or glycidamide to nucleophilic sites of macromolecules, especially SH-groups, appears to be the biochemical cause for the neurotoxic effects of acrylamide. A summary of the mechanism discussed can be found in Friedman (2003).

2.2 Carcinogenicity

The carcinogenic and the genotoxic effects of acrylamide are presented in detail in the MAK documentation (Greim 2007, translated).

In long-term carcinogenicity studies in rats and mice, in which acrylamide was administered orally, cutaneously or intraperitoneally, increased incidences of cancer localized at different sites were observed. In female rats, these consisted of malignant and benign mammary tumours, tumours of the central nervous system, the thyroid gland, pharynx, clitoris and uterus. In the males, mesotheliomas of the

tunica vaginalis testis and scrotum, and tumours of the thyroid gland were found. The doses at which increased cancer incidences from acrylamide were found are in the range between 0.1 and 2 mg/kg body weight/day.

Mice react to tumour induction more sensitively than rats. This should especially be attributed to the fact that approximately three times higher quantities of glycidamide are formed by mice in their metabolism than by rats. Glycidamide turned out to be the ultimate carcinogen of acrylamide (Rice 2005).

To clarify the question whether acrylamide is also carcinogenic in humans, a number of epidemiological studies were carried out in cohorts exposed to acrylamide at the workplace. The acrylamide concentrations in the air at the workplaces were between 0.1 and 1 mg acrylamide/m³. Relationships between acrylamide exposure and the occurrence of cancer diseases could thereby not be demonstrated (Collins et al. 1989; Marsh et al. 1999; Sobel et al. 1986). However, these studies were regarded as not being suitable to answer the question as to the possible carcinogenic effect of acrylamide in humans, as the investigated cohorts were too small among other factors. In addition, there were considerable deficits in the assessment of exposure (Greim 2007, translated).

The determination of exposure presents a major problem as to clarifying the question whether acrylamide is also carcinogenic in humans. Questionnaires are here frequently used. Their suitability for the determination of food uptake has not been found valuable in the field of environmental medicine. A valid assessment of changing habits, for example eating habits, is greatly dependent on the candidate's memory. This particularly applies for exposure parameters such as the Hb adduct of acrylamide, as this reflects exposure over the preceding four months. A precise evaluation of the foods ingested during this period is not possible using questionnaires (Kütting et al. 2005). In addition, other variables influencing the acrylamide level exist such as age, sex and season.

Owing to the small number of persons investigated and other shortcomings, the statistical power of the environmental medical studies available is too low (Mucci et al. 2003, 2004; Pelucchi et al. 2003) for a correct assessment of the internal exposure which could provide an association with possible cancer incidences.

3 Exposure and Effects

In the People's Republic of China, 41 workers employed in the catalytic production of acrylamide from acrylonitrile were investigated with regard to their internal acrylamide exposure in 1993. The haemoglobin adducts of acrylamide and acrylonitrile were determined. The AAVal values were between 8.6 and 972.4 µg/l. For the first time, GAVal in blood was also determined. According to this investigation, the GAVal values were equally high or somewhat higher than the AAVal values (54.9–1 098 µg/l). From these results, the authors calculated that the workers with the highest exposure to acrylamide absorb about 3 mg/kg body weight and day, and

compared this with the dose of 2 mg/kg body weight and day administered to rats, which already produced an increase in tumour incidences (Bergmark et al. 1993). The same workers were examined in 1994 to find out whether relationships between Hb adduct levels, mercapturic acid excretion in the urine and neurological effects can be derived. The observed and measured neurological deviations were summarized in a "neurotoxicity index", which correlates well with mercapturic acid excretion and the concentration of Hb adducts. About 70% of the workers showed symptoms of peripheral neuropathy.

In connection with the "tunnel accident" in Sweden in 1997, in which workers were exposed to acrylamide, a working group investigated 210 involved persons with regard to their internal acrylamide exposure and a number of neurophysiological effects. 47 workers showed acrylamide-Hb adduct levels in the blood within the normal background range of the general population (0.6–2.0 mg/l). The remaining 163 workers displayed increased acrylamide-Hb adduct levels between 2.0 and 506.2 mg/l. A strong association between AAVal concentration and symptoms of the peripheral nervous system, such as formication and feelings of numbness in hands and feet, was established. For these peripheral neurological effects the authors derive a NOAEL of 14.6 mg AAVal/l blood (Hagmar et al. 2001). In the neurophysiological examination, standardized methods were applied which covered the testing of motor and sensory nerves of the right extremities.

The external and internal acrylamide exposure of 62 employees engaged in the manufacture of polyacrylamide based products for applications in water treatment as well as in paper, paint and textile processes was subject of a study carried out in the UK. 260 acrylamide measurements were obtained using personal air samples. A total of 275 pre-shift and 247 post-shift urine samples were collected. These were subsequently examined for the mercapturic acid concentration of acrylamide (AAMA). The concentration of acrylamide in the air at the workplaces was on average below 0.03 mg/m³. A significant association was found between ambient air concentration and the concentration of mercapturic acid in urine. From these data the authors derive a "Biological Monitoring Guidance Value" (BMGV) of 8.3 mg AAMA/g creatinine. This value corresponds with the 90th percentile of the observed AAMA elimination in the workers. No difference was made between smokers and non-smokers in deriving this limit value (Bull et al. 2005). It must be pointed out that the highest AAMA concentration in the urine of a control person who was a tobacco smoker was higher at 8.9 mg AAMA/g creatinine.

In a further study from the UK partly by the same authors and probably also comprising the same persons exposed to acrylamide, it was investigated whether there was a relationship between the acrylamide concentration in the ambient air and the acrylamide-Hb adduct concentration in blood. A close correlation between both parameters was found (Jones et al. 2006).

4 Selection of Indicators

Basically, the Hb adducts and the mercapturic acids of the reductive and oxidative metabolism are available for the biological monitoring of persons exposed to acrylamide. These are on the one hand

- N-(2-carbonamideethyl)valine (AAVal) and
- N-acetyl-S-(2-carbonamideethyl)cysteine (AAMA) formed by direct attachment of the N-terminal valine of haemoglobin or glutathione to acrylamide.

On the other hand, glycidamide also reacts with haemoglobin and glutathione to form

- N-(R,S)-(2-carbonamide-2-hydroxyethyl)valine (GAVal) and
- N-(R,S)-acetyl-S-(2-carbonamide-2-hydroxyethyl)-L-cysteine (GAMA).

As glycidamide is the ultimate carcinogen of acrylamide, this means that GAVal and GAMA are the best suitable parameters for the assessment of exposure to or effects of acrylamide.

Unfortunately, these two parameters have up to now been used in a few studies only. No reliable data on the investigation of persons occupationally exposed to acrylamide are available at present.

In contrast, studies have been carried out in which the Hb adduct of acrylamide was determined in the blood of persons occupationally exposed to acrylamide as well as in that of the general population. As there is a close relationship between AAVal and GAVal, AAVal can be used as a suitable parameter for exposure or effect. On average, the concentrations of the Hb adducts of acrylamide and glycidamide in humans are at a ratio of 1:1 (Schettgen et al. 2003, 2004 b).

As far as the elimination of the mercapturic acid from the unchanged acrylamide is concerned, the data are also not sufficient to be used for the assessment of internal acrylamide exposure of occupationally exposed persons.

5 Methods

For the analysis of N-(2-carbonamideethyl)valine (AAVal) from haemoglobin, a tested method is available from the Commission which has already been approved and published (Bader et al. 2010, translated). To determine AAVal, the erythrocytes are first separated from the whole blood. After haemolysis of the erythrocytes, the globin is separated from the haemoglobin. In a modified Edman degradation, the terminal valine of the haemoglobin is separated off and simultaneously derivatized. The acrylamide is bound to this valine. Using capillary gas chromatography, the analyte is separated from attendant substances and determined by mass spectrometry. A dipeptide, N-(2-carbonamideethyl)valine-leucine-anilide, is used for calibration. Methods such as this one, used to determine Hb adducts of carcino-

genic substances, are relatively elaborate, but have now become routine in appropriately equipped laboratories and can be carried out with reliable results.

6 Background Exposure

The non-smoking general population takes up acrylamide almost exclusively via food (Böttcher et al. 2006 a). Other absorption pathways and sources, such as cosmetic products, drinking water, and the residual monomeric contents of paints and soil improving agents, are of minor importance (EU 2002; Madle et al. 2003). Greater quantities of acrylamide are taken in via smoking tobacco than with the food. Increased acrylamide uptake via passive smoking is also confirmed.

A series of investigations are available in which the concentration of the acrylamide-Hb adduct in blood samples from the population were measured. In 1997 it was described for the first time that AAVal can be found in practically all blood samples from the general population (Bergmark 1997). In eight occupationally non-exposed non-smokers the author found a mean AAVal concentration of 0.87 µg/l. Non-exposed smokers on the other hand showed an AAVal concentration which was on average four times higher (3.32 µg/l) ($n = 10$). In 18 non-exposed non-smokers in another study AAVal values between 0.57 and 2.0 µg/l were found (Hagmar et al. 2001). In an investigation of 62 persons from the German general population, AAVal concentrations between <0.34 and 1.4 µg/l were measured (median: 0.6 µg/l) in non-smokers. Also in this collective, smokers were found to have a six times higher AAVal concentration in blood. The values for smokers were between 0.37 and 8.4 µg/l (median: 2.4 µg/l) (Schettgen et al. 2003). In a larger study of the German general population ($n = 395$) the non-smokers ($n = 296$) were found to have a mean AAVal level of 0.4 ± 0.2 µg/l (range <0.3–1.2 µg/l) (Bader et al. 2005). In this case too, the corresponding mean value for smokers ($n = 99$) was approximately four times higher: 1.5 ± 1.4 µg/l (range: <0.3–12 µg/l). Investigations of a population group in Bavaria of in total 1 008 persons revealed a median value of 0.72 µg AAVal/l blood in non-smokers ($n = 857$). The smokers ($n = 148$) had a median value of 1.8 µg/l blood. The maximum values for non-smokers and smokers were 2.8 and 9.0 µg AAVal/l blood, respectively (Kütting et al. 2009).

The daily acrylamide intake can be calculated from the Hb adduct levels (Calleman 1996; Fennal et al. 2005). Taking the data of the Bavarian study as a basis, the mean acrylamide intake of non-smokers is 0.41 µg/kg body weight/day, and that of smokers 1.15 µg/kg body weight/day. The maximum values are 1.36 and 4.83 µg/kg body weight and day, respectively (Kütting and Drexler 2007; UBA 2008).

7 Evaluation

With the haemoglobin adduct of acrylamide, N-(2-carbonamideethyl)valine (AAVal), a parameter is available which reflects the internal exposure to/effect of acrylamide in a diagnostically reliable, specific and sensitive way. Due to the efficient absorption of acrylamide through the skin, however, no useful correlation between the acrylamide concentration measured in the air and the AAVal level in blood can be derived. From occupational medical examinations, it is possible to deduce that no neurotoxic effects of acrylamide are to be expected below a concentration of 14.6 µg N-(2-carbonamideethyl)valine/l blood. Therefore, a BLW of

15 µg N-(2-carbonamideethyl)valine/l blood¹⁾

is established.

The sampling time is not fixed.

8 Interpretation of Results

Eating and smoking habits in particular have to be determined by anamnesis for a better interpretation of N-(2-carbonamideethyl)valine concentrations. The background exposure of the general population has been determined to be maximum 2.8 µg AAVal/l blood for non-smokers and 9.0 µg AAVal/l blood for smokers.

Otherwise, the general principles for the assessment of biomonitoring results apply.

At present no special guidelines by the Berufsgenossenschaft (Employers' Liability Insurance Association) and no special recommendation for the performance of preventive occupational medical check-ups in persons occupationally exposed to acrylamide exist.

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1) No longer valid. For updated values please refer to
<http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

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