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Acrylonitrile – Addendum for evaluation of a BAR

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

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BAR (2009)	**0.3 µg N-(2-cyanoethyl)valine/l blood**[a)] Sampling time: not fixed
MAK value	**not established**
Absorption through the skin (1958)	H
Carcinogenicity (1977)	Category 2

a) evaluated for non-smokers

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Re-evaluation

Acrylonitrile [107-13-1] was evaluated in 1993 (translated in Bolt and Lewalter 1995). At the time, establishment of EKA (exposure equivalents for carcinogenic substances) was not possible. Acrylonitrile was re-evaluated in 1996, and EKA were established (translated in Lewalter and Bolt 2010). The data on the derivation of a BAR (biological reference value) are now evaluated in the present addendum.

1 Metabolism and toxicokinetics

The available data show that acrylonitrile is absorbed at the workplace both by inhalation and percutaneously. In the List of MAK and BAT Values, it is therefore designated with an "H". Acrylonitrile is rapidly absorbed, distributed evenly throughout the body and metabolised to mainly form a glutathione conjugate. In studies with rats, it was found that 40–100% of an orally administered dose of acrylonitrile is excreted with the urine within 24 hours. 2–8% of the dose are excreted with the faeces and 7–15% exhaled via the lungs in the form of HCN, CO_2 or unchanged acrylonitrile (Léonard et al. 1999).

For acrylonitrile, the direct bonding to glutathione (reductive pathway) and the resultant mercapturic acid represent a large part of the metabolites excreted with the urine. The amount of this mercapturic acid in the metabolites excreted with the urine is approximately 40% in rats and approximately 25% in mice (Sumner et al. 1997). Acrylonitrile is converted to the corresponding epoxide i.e. cyanoethylene epoxide via cytochrome P450 2E1 (Sumner et al. 1999). Altogether, the reaction products of this highly reactive metabolite represent with 60–80% the majority of all metabolites excreted with the urine. Cyanoethylene epoxide can be degraded by conjugation with glutathione at position 2 to N-acetyl-S-(1-cyano-2-hydroxyethyl)cysteine. In rats, this mercapturic acid represents approximately 13% of the metabolites excreted with the urine (in mice: about 9%) (Sumner et al. 1997).

From the glutathione conjugation at position 3, an unstable cyanohydrin results, which reacts to intermediary S-(2-oxoethyl)glutathione under cleavage of cyanide. This can be excreted in the form of N-acetyl-S-(2-hydroxyethyl)cysteine after reduction. With 30% in the rat (16% in the mouse) this non-specific mercapturic acid represents the second most important urinary metabolite. The cyanide formed hereby is converted to thiocyanate via the enzyme rhodanase (thiosulfate sulfurtransferase), and is also excreted with the urine as such (Sumner et al. 1997). This formation of cyanide in the metabolism is considered to be closely associated with the acute toxicity of acrylonitrile (Léonard et al. 1999; Thier et al. 1999).

The activity of the glutathione transferases plays an important role in the formation of cyanide, as occupational medical studies in accidentally exposed persons have shown. A low activity of the glutathione transferases accordingly causes a shift to oxidative metabolism, in the course of which cyanide is formed (Leng and Lewalter 2002).

Figure 1 shows the metabolism of acrylonitrile in F344 rats according to Sumner et al. (1997). Determination of the metabolites in urine after oral administration of ^{13}C-labelled acrylonitrile was carried out using ^{13}C-NMR.

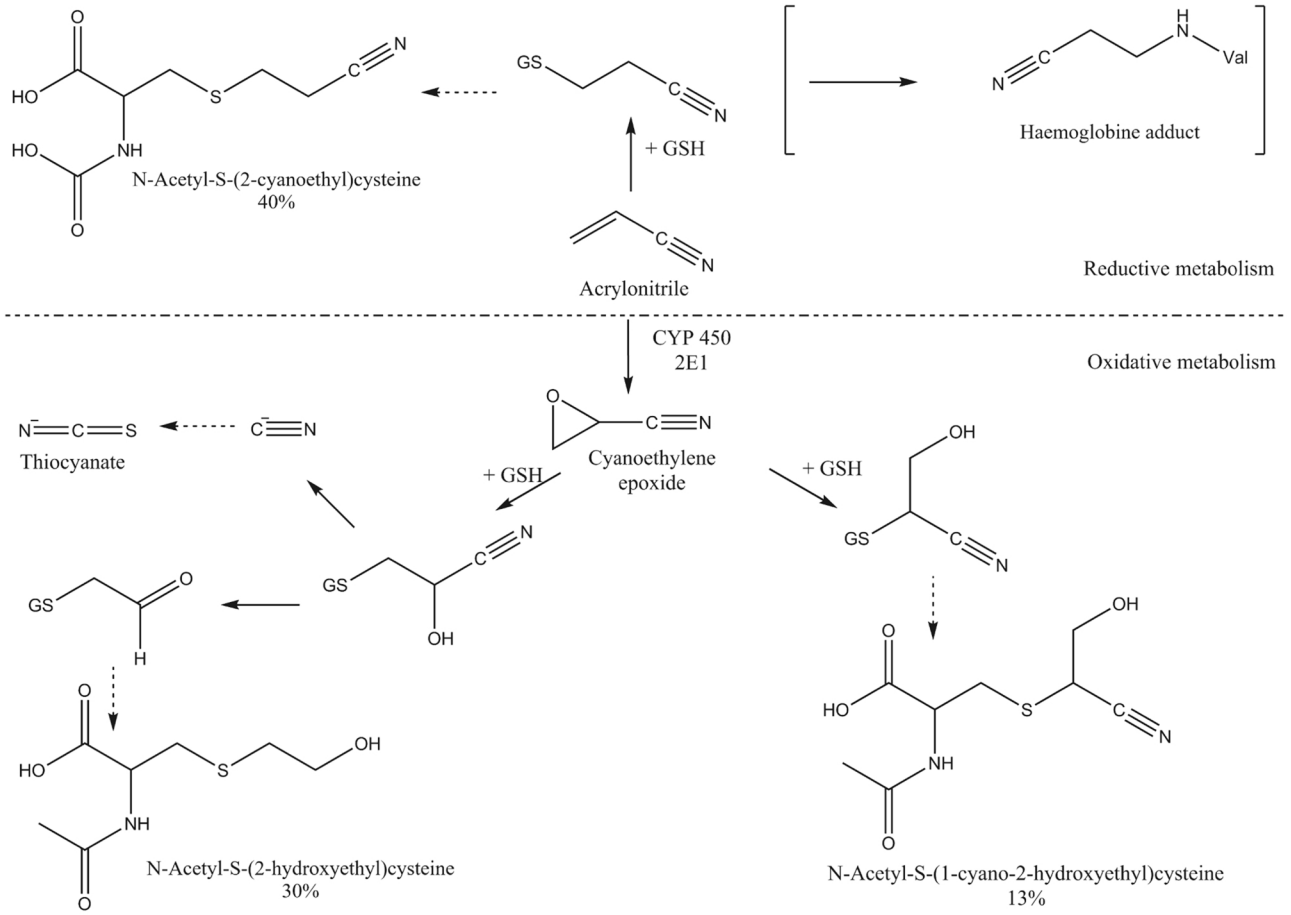

Fig. 1 Metabolism of acrylonitrile in F344 rats modified after Sumner et al. (1997). The percentages refer to the proportion of metabolites detected in urine.

By Michael addition of acrylonitrile to the N-terminal amino group of the valine in the haemoglobin, the adduct N-(2-cyanoethyl)valine is formed.

2 Critical toxicity

Acrylonitrile is acutely toxic, whereby symptoms similar to hydrocyanic acid poisoning, such as cyanosis, dizziness, vomiting and headache, can occur. The main additional effects are irritation of skin and mucous membranes as well as effects on the airways, gastrointestinal tract and the central nervous system. Severe intoxication can result in respiratory arrest. Initial acute symptoms after inhalation can already occur from concentrations of 16 ml/m^3. Long-term studies in exposed workers have revealed the presence of reduced glutathione levels in the liver, slightly changed liver values as well as sporadically reduced testosterone levels (Léonard et al. 1999). Acrylonitrile is sensitizing to the skin. It has therefore been designated with “Sh” in the List of MAK and BAT Values.

Acrylonitrile was found to be carcinogenic in a large number of animal studies. Epidemiological studies in exposed factory workers show, however, contradictory results: whereas, in a study from the USA, a significant increase in prostate cancer cases were recorded, the majority of studies published to date provide no indications of a causal relationship between exposure to acrylonitrile and an increased cancer incidence (Collins and Acquavella 1998; Greim 2007; Léonard et al. 1999).

Because of its clearly confirmed carcinogenicity in animal studies, the Commission has classified acrylonitrile in Carcinogen Category 2 (Greim 2007; Henschler 1978). The IARC has classified acrylonitrile in Category 2 B ("possibly carcinogenic to humans") in 1999 (IARC 1999).

3 Exposure and effects

3.1 Relationship between external and internal exposure

A correlation between the external exposure of acrylonitrile in the air and the concentration of N-(2-cyanoethyl)valine in erythrocytes was derived in the addendum 1996 (Lewalter and Bolt 2000). Since then, no new studies have been published.

3.2 Relationship between internal exposure and effects

Only very few studies exist in which biological effect monitoring was carried out after exposure to acrylonitrile. In addition, data on internal exposure are often lacking in these studies.

In the plasma of 49 workers exposed to 0.05–0.3 mg acrylonitrile/m^3, no significant difference in the expression of p53 and $p21^{WAF1}$ proteins could be found compared with a matched control group (Rössner et al. 2002).

In a further study with 30 male workers exposed to acrylonitrile, sperm density (75 × 10^6/ml versus 140 × 10^6/ml) and sperm count per ejaculum (205 × 10^6 versus 280 × 10^6) were significantly reduced compared with a control collective. In addition, in the comet assay, the sperm nuclei showed an increased tail moment (9.8 versus 4.3 µm) compared with the control group (Xu et al. 2003). Unfortunately, no data on the internal exposure of these workers are available.

In a further study, significant differences in the percentage of lymphocytes with aberrations in chromosome 1 as well as chromosome 4 were found in the lymphocytes of workers exposed to acrylonitrile compared with a control group (Beskid et al. 2006). Data on the internal exposure of the workers are again lacking.

To summarise, no relationship between internal exposure and effects can be derived at present due to the lack of data on acrylonitrile.

4 Selection of indicators

The most widespread method for biomonitoring acrylonitrile is the specific determination of the covalent adducts in human haemoglobin (Hb), particularly N-(2-cyanoethyl)valine.

In the literature, the adduct concentration of N-(2-cyanoethyl)valine is mostly cited as pmol/g globin. For reasons of practicability, results are usually determined in µg/l blood. For such a conversion, it is assumed that the average globin concentration in blood is approximately 144 g/l (Bunn 1992) and that the contribution of the four haem groups to the total molar mass of haemoglobin of 64 kDa can be neglected.

Conversion is based on the following formula:

$$\text{adduct level}\,[\text{pmol/g globin}] = \frac{\text{adduct level}\,[\text{µg/l blood}]}{\text{MM of N-alkylvaline}\,[\text{µg/pmol}] \times \text{globin level in blood}\,[\text{g/l}]}$$

MM = molar mass

Using MM N-(2-cyanoethyl)valine = 169.2 g/mol = 169.2 × 10^{-6} µg/pmol, the following conversion factor is obtained:

$$\text{N-(2-cyanoethyl)valine}\,[\text{µg/l blood}] = \text{N-(2-cyanoethyl)valine}\,[\text{pmol/g globin}] \times 0.025$$

By the determination of the Hb adducts, the exposure during the 120 days before sampling (lifetime of erythrocytes) is also recorded. The Hb adduct level is directly correlated with the concentrations of corresponding DNA adducts, which can be regarded as the initial starting points for a chemically induced carcinogenesis (Angerer 2001; Ehrenberg et al. 1983).

For this determination, erythrocyte lysate is required as test material.

The determination of unchanged acrylonitrile as well as metabolically formed cyanide in blood cannot – both due to a lack of data and to rapid elimination – be recommended for biomonitoring, and is merely useful in cases of acute acrylonitrile intoxication for treatment control following accidents (Leng and Lewalter 2002).

5 Analytical Methods

To determine the acrylonitrile haemoglobin adduct (N-(2-cyanoethyl)valine), a method tested and published by the Commission is available (van Sittert et al. 1997). In modified form, it has already been used in various studies (Bader et al. 2005; Kütting et al. 2008; Schettgen 2009; Schettgen et al. 2002). From the erythrocyte haemolysate 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. Thereby, the alkylated N-terminal valine is cleaved from the protein chain and converted to the corresponding pentafluorophenyl thiohydantoin derivative. The derivatives obtained are extracted from the protein matrix by liquid-liquid extraction with diethyl ether and separated from interfering substances through subsequent washing steps. After capillary gas chromatographic separation, detection and quantification is performed using mass spectrometry in the EI mode or NCI mode.

6 Background exposure

The consumption of tobacco products is one of the main sources of exposure to acrylonitrile in the general population. Acrylonitrile has been identified as a component of tobacco smoke. The determined amounts in smoke were 3–15 µg acrylonitrile per cigarette. Highly significant correlations were found between the anamnestically reported number of cigarettes smoked daily and the quantified amount of N-(2-cyanoethyl)valine in the smokers' blood. Accordingly, one cigarette smoked per day increases the N-(2-cyanoethyl)valine level by approximately 6.1–8.5 pmol/g globin (~ 0.2 µg/l blood) (Fennell et al. 2000; Schettgen et al. 2002).

In persons with "smoker status" reported in the anamnesis, the median values of the adduct levels were in the range of 56–131 pmol/g globin (1.4–3.3 µg/l blood) (Bader et al. 2005; Bergmark 1997; Perez et al. 1999; Schettgen 2009; Schettgen et al. 2002). The 95th percentiles of the values measured are in the range of 146–332 pmol/g globin (3.7–8.3 µg/l blood) (Bader et al. 2005; Bergmark 1997; Schettgen 2009; Schettgen et al. 2002). Markedly higher values were, however, given by Fennell et al. (2000); for heavy smokers with a daily cigarette consumption of two packs per day, the mean value was 364 pmol/g globin (9.1 µg/l blood) (see Table 1).

Tab. 1 Concentration of N-(2-cyanoethyl)valine in the blood of persons having no occupational contact with acrylonitrile

Collective	N-(2-cyanoethyl)valine [pmol/g globin]			References
	Median	95th p	Range	
NS (n = 8)	< 2	< 2	< 2	Bergmark 1997
S (n = 10)	110	175	25–178	
NS (n = 18)	0.76[a)]		0.32–1.6	Perez et al. 1999
"passive smokers" (n = 3)	1.1[a)]		0.6–1.7	
"party smokers" (n = 3)	8.6[a)]		2.2–14.6	
NS (n = 14)	4.9 (± 1.9)[a)]			Fennell et al. 2000
S (1 pack/day) (n = 18)	252 (± 22)[a)]			
S (2 packs/day) (n = 14)	364 (± 34)[a)]			
NS (n = 24)	< 4	14	< 4–71	Schettgen et al. 2002
S (n = 38)	131	241	12–256	
NS (n = 273)	< 4	7	< 4–26	Bader et al. 2005
S (n = 97)	56	146	< 4–179	
NS (n = 591)[b)]	< 4	< 4	< 4–3	Schettgen 2009
"passive smokers" (n = 98)[b)]	< 4	< 4	< 4–9	
S (n = 144)	81	332	< 4–607	

NS: non-smokers; S: smokers; 95th p: 95th percentile
[a)] mean value (standard deviation)
[b)] aged 18–65 years

In how far exposure to passive smoking plays a role for the non-smoking general population has at present still not been clarified conclusively. One publication citing three "passive smokers" indicates an association between the haemoglobin adduct level and exposure to passive smoking (Perez et al. 1999). In contrast, in a larger study with 98 "passive smokers" only a few cases (5) were above the detection limit (Schettgen 2009).

In persons where "non-smoker" status is reported in the anamnesis, generally no acrylonitrile adducts could be found in the blood in any of the studies at a detection limit of 4 pmol/g globin (0.1 µg/l blood). In addition, the 95th percentile was below the detection limit for these groups (Bergmark 1997; Schettgen 2009) or close to the detection limit at 7 pmol/g globin (Bader et al. 2005) and 14 pmol/g globin (Schettgen et al. 2002). Sporadically, in spite of a status as "non-smoker", maximum values up to 13 pmol/g globin (Schettgen 2009), 26 pmol/g globin (Bader et al. 2005) and 71 pmol/g globin (Schettgen et al. 2002) were determined. These could possibly be attributed to occasional tobacco consumption, such as were also described for "party smokers" with N-(2-cyanoethyl)valine concentrations of up to 15 pmol/g globin (0.37 µg/l blood) (Perez et al. 1999) (see Table 1).

A further possible exposure source for the general population can be found in residues of monomeric acrylonitrile in the respective textile fibres or plastic products, some of which are also used in food packaging. The residues here found in acrylic fibres were generally markedly below 1 mg/kg (Schettgen 2006). Based on these data, it is possible to conclude that the contribution of exposure to acrylonitrile from residues in textile fibres is negligibly small for the consumer.

According to the Consumer Goods Ordinance (Bedarfsgegenständeverordnung), the maximum tolerable migration limit of acrylonitrile from respective plastic packaging into packed foods (ABS plastic, acrylonitrile-butadiene-styrene copolymerisate) is 0.02 mg acrylonitrile/kg food (BMG 1998). Assuming that a maximum 5% of the foods for human consumption are packed in respective plastic elements, plus an average daily food consumption of 2 kg,

a maximum absorption of 2 µg acrylonitrile/day or about 0.03 µg/kg body weight and day would thus be present in such a "worst-case" situation (EU 2004).

In an earlier study on atmospheric exposure in industrial regions of Germany during the period 1977–1984, acrylonitrile concentrations in the air were determined. In municipal areas concentrations of 0.01–10.4 µg/m³ were measured, whereas the concentration in the air of rural areas was generally below 0.002 µg/m³ (EU 2004). With the exception of the extreme values measured, this source of exposure can be considered negligible for the general population.

To summarise, it can be concluded that, as regards the individual internal exposure of the normal population to acrylonitrile in Germany, smoking habits play a decisive role. In this context, a thorough anamnesis of individual smoking behaviour (number of cigarettes smoked per day) must be undertaken in the persons investigated, especially where occasional smoking is involved. This is because, due to the long lifetime of erythrocytes, previous exposures are also determined in the analysis.

7 Evaluation of the BAR

Owing to the strong effects of smoking habits on the N-(2-cyanoethyl)valine level (Section 3), non-smokers and smokers must be considered separately. In order to derive a BAR, at present, the data given by Schettgen et al. (2002) and Schettgen (2009) or by Bader et al. (2005) are to be used in particular. These studies included large numbers of volunteers compared with other publications.

The median of the acrylonitrile adduct in the blood of non-smokers was below the detection limit of 4 pmol N-(2-cyanoethyl)valine/g globin (0.1 µg/l blood) in all of these studies. The 95th percentile in these groups was also either below (Schettgen 2009) or close to the detection limit, i.e. at 7 pmol/g globin (Bader et al. 2005) and 14 pmol/g globin (Schettgen 2006).

Taking the uncertainty regarding smoking in the anamnestic data into account, from the data of the adult, **non-smoking** general population of Germany

a BAR of 0.3 µg N-(2-cyanoethyl)valine/l blood

is established for acrylonitrile. This approximately corresponds to a value of 10 pmol/g globin.

8 Interpretation of Results

When interpreting results, smoking habits (exposure to passive smoking/"party smoking" if and where necessary) are to be included in particular.

The maximum value for the adult **smoking** general population of Germany was determined to be about 600 pmol/g globin (**15 µg N-(2-cyanoethyl)valine/l blood**).

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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