

# Reassessment of the Toxicity of Acrylamide

Current research yields no evidence for genotoxicity at consumer-relevant intake level and proves endogenous exposure to acrylamide.

It's almost 19 years since a Swedish research group accidentally came across the now comprehensively investigated substance Acrylamide (AA) in food and discovered it to be a process contaminant, i.e. as a contaminant that arises during the production process of food. Acrylamide is formed in the Maillard reaction from the free amino acid Asparagine and certain reducing sugars (Glucose and Fructose). It is generated during baking, roasting and deep-frying under dry conditions at temperatures above 120°C and is found in products such as potato chips, French fries, bread, cookies and coffee.

For information about the legal developments relating the process contaminant Acrylamide both at National and European level refer to <https://www.lci-koeln.de/deutsch/veroeffentlichungen/lci-focus/15-years-of-minimising-acrylamide-in-foodstuffs>.

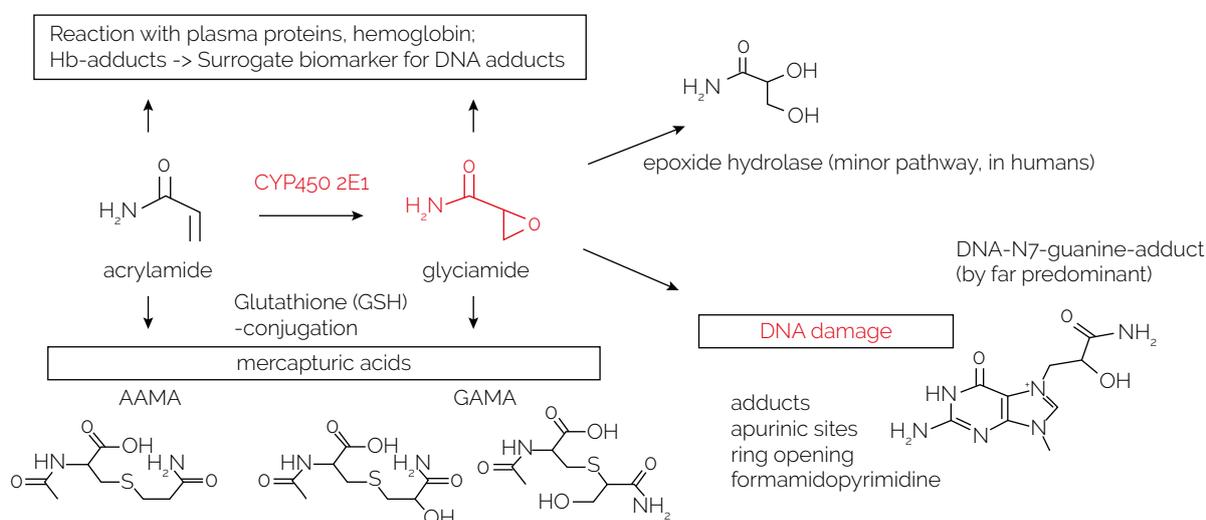
Discussions are right now ongoing at EU level to lower the so-called indicative values currently in force and to set binding maximum values for certain foods.

From a toxicological point of view, the intake of high amounts of Acrylamide can be classified as relevant: In 1994, the IARC (International Agency for Research on Cancer) classified Acrylamide in Category 2A, probably carcinogenic in humans. It was assumed that the carcinogenic effect of AA is primarily based on its metabolic oxidation to the genotoxic metabolite Glycidamide (GA). Both AA and GA are highly reactive and can form covalent bonds in the organism with numerous biomolecules, such as amino acids, peptides (main representatives Glutathione, GSH), with plasma proteins such as Albumin and with the blood pigment Hemoglobin (Hb) in the red blood cells.

Such reactions with endogenous substances, in which the reaction with Glutathione (GSH) is in the spotlight, are considered detoxification reactions. They contribute to the fact that a significant proportion of the AA ingested is detracted from metabolic activation to genotoxic GA (figure 1). GSH adducts of AA or GA are metabolically converted to the corresponding mercapturic acids (MA) and excreted in the urine.

## Previous assessment

EFSA shared the IARC's assessment so far, since human studies have provided limited and contradicting evidence of an increased risk of cancer, but laboratory animal studies have shown that exposure to AA in feed increased the likelihood of developing gene mutations and tumors in various organs. EFSA's experts agreed with previous assessments that AA in food could increase the risk of developing cancer in consumers of all ages.



Metabolism of acrylamide in the human body: toxification / detoxification [Eisenbrand, G Neues zur Prozesskontaminante Acrylamid, WpD Moderne Ernährung heute, Nr. 1, Februar 2019]

This applies to all consumers, with children (based on body weight) being the most exposed age group. In 2015, EFSA published its first full risk assessment on AA in food. The panel concluded that current levels of dietary AA exposure are not of concern in terms of non-carcinogenic effects. Although AA has not been proven to be carcinogenic in humans, the margins of exposure (MOEs) indicate possible carcinogenic effects based on animal experiments.

### Revision of the toxicity assessment

In 2019, toxicity studies on AA carried out by scientists from the University of Kaiserslautern, led by the toxicologist Professor Dr Gerhard Eisenbrand, turned over a new leaf. From the evaluation of various up-to-date studies, he concluded that the current research shows no evidence for genotoxicity in the case of consumer-relevant intake of AA from food and Prof. Eisenbrand also confirmed an endogenous AA exposure that is equivalent to that from food intake.

Just like previous risk assessments, Eisenbrand assumes that both AA and GA are highly reactive and form bonds with numerous biomolecules in the organism – especially with Glutathione (GSH). In addition, adducts with Hemoglobin were found in the erythrocytes at a mean intake of AA (50-100 µg / kg body weight). These reactions are used for detoxification and contribute to the fact that a considerable proportion of the ingested AA is detained from metabolic activation to genotoxic GA. In addition, the GSH coupling ensures that the GA formed in the liver is effectively detoxified in consumer-relevant levels of exposure.

The epidemiological studies considered by Eisenbrand showed no connection between increased cancer risk and diet-related AA exposure in humans. The results also allowed the conclusion that in the lower, consumer-relevant intake range (up to 100 µg / kg body weight in rats), no genotoxicity of AA via metabolic GA formation is to be expected and tumor formation in the range of higher doses due to the genotoxicity



of GA is proven. The presumed genotoxic key metabolite of AA, namely GA, in addition reveals a rather poor mutagenicity, which mainly induces effects known to show rather low (or nonexistent) mutagenic activity at biologically relevant doses.

Furthermore, results from animal experiments and controlled intervention studies in humans show that AA is not only absorbed, but is also formed endogenously ("in the body itself"). Controlled intervention studies also confirm this hypothesis in humans, for whom the endogenous exposure is comparable to the average consumer exposure via food. It is generally known that also other process contaminants can be formed by ordinary metabolic activities.

According to Eisenbrand, these new findings do not support the theory of a genotoxic mechanism of action when it comes to AA in humans and animals. While AA itself is undoubtedly non-genotoxic, the epoxide GA formed by metabolic conversion can cause DNA damage through covalent bonding. However, there is insufficient evidence to support this theory. The genotoxicity of AA occurs only at excessively high doses that are not relevant to the consumer at a normal level of dietary exposure. A non-genotoxic mechanism might be responsible for the tumor formation in rodents on which the presumption of genotoxicity of AA is based, which is to be regarded as species-specific

for rodents and therefore does not apply to humans.

It should be noted that a comparison of metabolic kinetics in laboratory animals (rodents) and humans indicates that GA formation in mice (less pronounced in rats) is significantly faster than in humans. Conversely, the detoxifying GSH coupling takes place faster in humans.

In summary, the new findings on toxicity and the endogenous formation of AA support a revision of the risk assessment towards the setting of a tolerable daily intake dose (TDI) based on a NOAEL value (no observed adverse effect level). The very interesting question is, however, whether and when these new, significant and even revolutionary findings will lead to a rethinking in the minds of EU risk managers and by that will find their way into the current discussions on maximum levels of the Commission.



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