Questions and Answers on Pyrrolizidine Alkaloids in Food

Updated BfR FAQ of 16 December 2022

A few years ago, high levels of 1,2-unsaturated pyrrolizidine alkaloids (PA) were detected in tea and herbal tea. High concentrations of these compounds can also occur in certain honeys, depending on their origin. Moreover, leafy salads and herbs/spices may be contaminated with parts of plants containing PA, such as *Senecio vulgaris* (ragwort, groundsel), which contain significant amounts of 1,2-unsaturated PA. Food supplements made from or containing plants with a PA content may represent another source.

1,2-unsaturated PA are undesirable in food and feed, due to their harmful effects to human health. In the opinion of the BfR, further measures are needed, especially by the food industry, to reduce the contamination of foods with 1,2-unsaturated PA. The BfR has compiled questions and answers on this subject.

What are pyrrolizidine alkaloids?

Pyrrolizidine alkaloids (PA) is the name for a large group of natural substances which are mainly produced by plants, but also by fungi and bacteria. It is assumed that certain plant species produce these compounds in order to ward off predators. There are currently several hundred known PA and related *N*-oxides. PA have been detected in over 350 plant species worldwide so far, but based on chemotaxonomic considerations, the occurrence in more than 6,000 plant species is expected. The ability to form PA is found in representatives of at least 13 plant families, in particular in representatives of the composite family (*Asteraceae*), the borage family (*Boraginaceae*), the legume family (*Fabaceae* or *Leguminosae*), and the dogbane family (*Apocynaceae*), the buttercup family (*Ranunculaceae*) and the figwort family (*Scrophulariaceae*). Examples of indigenous PA-producing plants are common ragwort, common groundsel and viper's bugloss. Chemically speaking, PA are esters composed of a necine base and aliphatic mono- or dicarboxylic acids (necine acids).

Are there health risks for consumers from foods that contain PA?

Certain PA may damage the liver. In addition, a mutagenic (genotoxic) and cancer-causing (carcinogenic) potential was demonstrated in animal experiments for some derivatives. These effects are caused by PA in which the necine base has a 1,2-unsaturated necine structure and is esterified with at least one branched necic acid. These compounds, known as 1,2-unsaturated PA, are undesirable in food and feed because of their potential to be harmful to health. The BfR has carried out an assessment of possible health risks from 1,2-unsaturated PA in foods. This was based on an estimate of the total intake using current occurrence data (period 2015-2019) for the following food groups: Honey, various teas and herbal teas, milk and spinach.

It was shown that the estimated total chronic exposure via the food groups considered in the scenarios considered for children and adults leads to intake levels that may be regarded as being of low concern. However, exposure to 1,2-unsaturated PA can still occur via other foods that could not yet be taken into account in the estimate of the total intake. These include, for example, herbs/spices and food supplements that are manufactured on the basis of PA-forming plants or bee products such as pollen. A provisional estimate of the PA intake via herbs/spices, for example, indicates that despite the small amounts consumed, these could make a toxicologically relevant contribution to long-term and short-term exposure to 1,2-unsaturated PA.

Are cases of poisoning by 1,2-unsaturated PA known?

Severe, sometimes fatal poisoning is repeatedly observed in humans after ingestion of high doses of 1,2-unsaturated PA. For example, several thousand cases of endemically occurring poisoning have been documented in Afghanistan in recent decades. The cause of the cases of poisoning was the consumption of cereals contaminated with parts of plants from PA-producing *Heliotropium* species. In Jamaica, cases of poisoning occurred as a result of so-called bush teas, which contained parts of *Crotalaria* and ragwort plants. In Asia, poisoning is also associated with the consumption of certain herbs used in traditional Chinese medicine that either contain 1,2-unsaturated PA themselves or are confused with plants containing PA or are contaminated with them. A case of poisoning was also reported to the BfR by treating physicians, in which an adult developed a severe liver function disorder after eating plant parts which contained 1,2-unsaturated PA (medical disclosure of poisoning in accordance with §16e German Chemicals Act). PA-related poisonings are particularly characterised by veno-occlusive liver damage (and also of the lungs in rarer cases). Severe abdominal pain, pain in the liver region, loss of appetite, exhaustion, ascites, jaundice and liver enlargement have been observed as clinical symptoms of veno-occlusive damage to the liver.

However, with respect to the PA levels that are generally observed in Germany and Europe, acute poisoning has only been observed in certain individual cases. The health risks from a chronic intake are the main priority for the risk assessment.

Severe cases of poisoning have repeatedly observed in livestock after the animals have eaten plants containing PA. In beef cattle, for example, the occurrence of liver cirrhosis has been observed following intake of alpine ragwort from hay and silage. The intake of *Senecio* species containing PA while grazing is also known to have led to seneciosis in horses, which is characterised by liver-damaging effects.

What are the possible impacts on health as a result of long-term (chronic) intake of 1,2-unsaturated PA?

In the case of chronic intake, the liver is also the primary target organ for damage caused by 1,2-unsaturated PA. Veno-occlusive changes can also occur in this instance. Besides the liver, other organs - especially the lungs - may be damaged by long-term exposure. Long-term studies on rodents have also demonstrated that certain 1,2-unsaturated PA exhibit a carcinogenic potential. It is assumed that the carcinogenic effect is caused by mutagenic (genotoxic) effects. In general, no safe intake level can be derived with regards to this genotoxic-carcinogenic effect.

Are the results of studies on animals applicable to humans?

While there is substantial proof from numerous case reports that liver-damaging effects have also occurred in humans after short or medium-term intake of high doses of 1,2-unsaturated PA, there are no epidemiological studies which could provide information about the carcinogenic potential in humans. However, it should be noted that in many cases it is difficult to prove a corresponding association via epidemiological studies, since there can often be several decades between the intake of carcinogenic substances and the development of cancer in humans. However, the available scientific data indicates as a whole that the results from experiments on rodents for both liver-damaging and genotoxic-carcinogenic effects can be applied to humans.

How are potential differences in the carcinogenic potency of the numerous 1,2-unsaturated PA taken into account in the risk assessment?

In the case of 1,2-unsaturated PA, it is not the absorbed compounds themselves that are held responsible for the toxic effects, but certain metabolic products (so-called pyrrole metabolites). In general, the transformation into these reactive metabolites seems to be possible for all 1,2-unsaturated PA. For some derivatives of the 1,2-unsaturated PA this has already been proven experimentally.. However, since the absorption and metabolism of the individual compounds can differ depending on their respective structure, it can be assumed that this can have an impact on the potency of various derivatives of 1,2-unsaturated PA. Such differences have also been demonstrated experimentally for various 1,2-unsaturated PA. It is therefore being discussed whether and in what way the different potencies of individual 1,2-unsaturated PA and their *N*-oxides can be better taken into account in the future.

However, the BfR comes to the conclusion that the potency factors derived and proposed by various authors on the basis of the data currently available cannot yet be used sensibly for the assessment of possible health risks from 1,2-unsaturated PA. In particular, the potency factors proposed thus far do not yet allow any reliable conclusions to be drawn about the carcinogenic potency of various 1,2-unsaturated PA after oral ingestion in vivo. Therefore, when assessing the risk of cancer, all 1,2-unsaturated PA are currently grouped together. This assessment is in line with the assessment by the European Food Safety Authority (EFSA), which has also concluded that the current data still does not justify the use of potency factors for the risk assessment.

How can 1,2-unsaturated PA enter food?

Based on current knowledge, there are four ways in which 1,2-unsaturated PA can find their way into the human food chain:

1. A significant cause of the occurrence of 1,2-unsaturated PA in foods is PA-producing plants, which grow in the cultivation areas of crop plants and contaminate food during harvesting. For example, impurities in lettuce caused by ragwort/groundsel have been found in Germany. Increased concentrations of 1,2-unsaturated PA are known to occur in wheat from Afghanistan, caused by the strong spread of plants of the genus *Heliotropium* in wheat fields. The contamination of tea and herbal tea and herbs/spices with 1,2-unsaturated PA is also attributed to contamination of the raw materials which are harvested along with PA-producing plants.

2. Bee products, such as honey and pollen, may also be contaminated with 1,2-unsaturated PA. In particular, wild plants such as *Echium*, *Senecio* and *Borago* species, from which bees collect pollen, are considered to be sources of contamination. Raw honeys from certain countries of Central and South America have higher concentrations compared to those from several European countries.

3. 1,2-unsaturated PA can also find their way into food via contaminated feed given to livestock which then passes on to the foods produced from the animals, such as milk and eggs. However, there is currently no indication that foods of animal origin contain levels that would pose a health risk.

4. Another possibility is that food originates from plants that produce 1,2-unsaturated PA themselves. One such example is borage, also known as starflower. Borage, for exam-

ple, is used as a characteristic spice plant in the “Frankfurt Green Sauce”. Food supplements may also be manufactured using plants and parts of plants, or plant extracts, which contain 1,2-unsaturated PA themselves. For example, food supplements manufactured using hemp-agrimony are available in the form of capsules. This plant is a member of the composite family and is a known PA producer. In individual cases, concentrations of 1,2-unsaturated PA in such food supplements can be very high. By contrast, no 1,2-unsaturated PA have yet been detected in oil-based food supplements.

Can 1,2-unsaturated PA easily be detected analytically?

The analysis of 1,2-unsaturated PA is very complex, due to several naturally occurring individual compounds and their occurrence in different foods. However, because of their structure and chemical properties, it is generally very easy to analytically detect 1,2-unsaturated PA using liquid chromatography, in combination with mass spectrometry. The results of several round robin tests have demonstrated that both the detection methods used and the laboratories yielded satisfactory results, thereby demonstrating their suitability (*fitness for purpose*).

Which foods contribute most to the intake of 1,2-unsaturated PA in children and adults?

For children aged 6 months to 5 years, the intake of 1,2-unsaturated PA can essentially be traced back to herbal tea, rooibos tea and drinks containing herbal tea. Exposure for adolescents and adults also primarily comes from the consumption of herbal and rooibos tea. Moreover, exposure to 1,2-unsaturated PA also occurs via other foods which could not be considered in the current exposure assessment. Examples of these include herbs/spices and certain food supplements. The provisional estimate of the intake of PA via herbs/spices, for example, indicates that despite the small amounts consumed, these could make a toxicologically relevant contribution to long-term and short-term exposure to 1,2-unsaturated PA. Food supplements which exhibit high PA concentrations may also make a major contribution to the total intake of 1,2-unsaturated PA via food as an additional exposure source for adults.

Are there maximum concentrations (“limit values”) in the European Union for 1,2-unsaturated PA in foods?

Within the European Union, the general recommendation applies that exposure to mutagenic and carcinogenic substances should be minimised to the lowest level achievable by reasonable means (ALARA principle: *as low as reasonably achievable*), as even low intake quantities can result in an increased health risk, especially if consumed regularly.

In addition, in the EU, Regulation (EU) 2020/2040 sets maximum levels for pyrrolizidine alkaloids for certain foods, which have been in force since 1 July, 2022. Since then, foods with higher levels may no longer be marketed in the EU.

What meaning do the margin of exposure (MOE) concept and the MOE value have in the assessment of 1,2-unsaturated pyrrolizidine alkaloids?

It is sometimes claimed that the BfR has derived a guidance value for a ‘harmless intake’ of 1,2-unsaturated PA in its risk assessment. This is not the case. Instead, the BfR has used the margin of exposure (MOE) concept in its risk assessment, as it is generally done for genotoxic-carcinogenic substances in the EU. The MOE is the ratio calculated from a suitable toxicological reference point and the exposure to the substance in humans. In the case of 1,2-unsaturated PA, a so-called $BMDL_{10}$ of 237 µg/kg of bodyweight per day is currently being used as a reference point. A MOE of 10,000 or more is generally considered as being of low concern -

yet not harmless - with regards to public health, and therefore considered as low priority for risk management measures. The MOE concept is exclusively for the purposes of prioritising, i.e. estimating the urgency of risk management measures. It is not used for deriving *health-based guidance values*.

Indeed, maximum intake quantities resulting in a MOE of 10,000 can be calculated based on the $BMDL_{10}$. However, the conclusion that such values are of 'low concern' with regards to possible cancer risks cannot be equated with being 'harmless' from a toxicological perspective, as it cannot be safely concluded that there is no health risk, even with intake quantities within this range. The specification of such a maximum intake quantity up to a MOE of 10,000 is merely intended to illustrate from which intake quantity of 1,2-unsaturated PA the MOE falls below 10,000.

From the perspective of the BfR, which measures are necessary to reduce the contamination with 1,2-unsaturated PA?

In recent years, the food industry has taken various measures to reduce the levels of 1,2-unsaturated PA in various food groups. For example, this has already led to a reduction in concentrations in tea and herbal teas. Nevertheless, the BfR recommends continuing efforts to reduce the concentrations of 1,2-unsaturated PA in all food groups as far as it is technically feasible (ALARA principle). This applies in particular to food groups such as herbs/spices, whose occurrence data still occasionally show abnormally high concentrations.

The following points should be given particular consideration in this regard:

- A basic prerequisite for the safety of plant-based food is due care and attention in cultivating and harvesting the raw materials used for food production. For example, due to their distinctive appearances, ragwort species which may contain 1,2-unsaturated PA can be easily recognised, and therefore effectively monitored using suitable measures.

- Before marketing, sufficient monitoring should also be carried out by the food industry for all food groups concerned, especially herbal tea and tea batches as well as herbs/spices.

- The BfR advises applying the recommendations of the Codex Alimentarius in order to consistently minimise PA contamination of food. The recommendations appear in the "*Code of Practice*" on the topics of "*Management of the presence of PA-containing plants*" and "*Control of plant release and spread*".

What can consumers do in order to minimise the intake of 1,2-unsaturated PA?

The potential health risk for consumers can be reduced if they follow the general recommendation for variation and diversity in their choice of foods. By following this recommendation, a one-sided exposure to the various potentially health-damaging substances which must be expected to occur in low quantities in foods can be prevented.

- Parents in particular are advised not to only give their children teas and herbal teas but also to offer them other drinks, such as water or fruit juice diluted with water. Expectant and breastfeeding mothers should also alternate teas and herbal teas with other beverages. This also applies to people who satisfy their daily liquid requirement mainly in the form of herbal tea.

- When preparing salads, leafy vegetables and herbs, parts of plants which cannot be identified as known edible plants should be discarded as a matter of principle. The trend that can be observed in some groups of the population, of gathering herbs and other plants that grow in the wild in parks, forests and meadows and using them to make salads and green smoothies, may be associated with health risks, in the opinion of the BfR. Expertise is required here in order to avoid plants such as borage, coltsfoot and other plants that contain 1,2-unsaturated PA.

- Consumers who take food supplements based on bee pollen or plants that form 1,2-unsaturated PA should be aware that these products can contain higher levels of 1,2-unsaturated PA. This has been confirmed by data from the European Food Safety Authority (EFSA).

- Based on the current state of knowledge, there are no indications to suggest that animal-based foods contain 1,2-unsaturated PA in concentrations that would pose a health risk to consumers.