Risiken erkennen – Gesundheit schützen

Frequently asked questions on pyrrolizidine alkaloids in foods

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Some years ago, high levels of 1,2-unsaturated pyrrolizi-dinalkaloids (PA) were found 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 PAs, such as *Senecio vulgaris* (ragwort, groundsel), which contain significant amounts of 1,2-unsaturated PAs. Food supplements made from or containing plants with a PA content may represent another source.

Due to their harmful potential, 1,2-unsaturated PAs are undesired in food and feed. 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 PAs. The BfR has compiled questions and answers on this subject.

What are pyrrolizidine alkaloids?

Pyrrolizidine alkaloids (PAs) are 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 herbivores. There are currently several hundred known PAs and related *N*-oxides. PAs have been detected in over 350 plant species worldwide so far, but based on chemotaxonomic considerations, the occurrence of PA is expected in more than 6,000 plant species. The ability to produce PAs has been found in representatives of at least 13 plant families, especially in representatives of the composite (Asteraceae), borage (Boraginaceae), legume (Fabaceae or Leguminosae), dogbane (Apocynaceae), buttercup or crowfoot (Ranunculaceae), and figwort (Scophulariaceae) families. Examples of indigenous PA-producing plants are common ragwort, common groundsel and viper's bugloss. Chemically speaking, PAs are esters composed of a necine base and aliphatic mono- or dicarboxylic acids (necic acids).

Do foods containing PAs pose any health risks to consumers?

Certain PAs 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 PAs 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 undesired in food and feed due to their harmful potential. The BfR has carried out an assessment of possible health risks from 1,2-unsaturated PAs in foods. This was done on the basis of an exposure assessment, using current occurrence data (2015-2019 period) from relevant food groups.

It was found that the estimated total chronic exposure from all food groups under consideration resulted in intake levels in all considered scenarios for children and adults at which health risks were considered to be unlikely. However, exposure to 1,2-unsaturated PAs still occurs via other foods, something which could not be considered in the current exposure assessment. Examples of these include herbs/spices and food supplements. A preliminary estimation of the PA intake via herbs/spices indicates, for example, that despite the small quantities consumed, these can contribute significantly to both long-term and short-term exposure to 1,2-unsaturated PAs.

Are there known cases of poisoning with 1,2-unsaturated PAs?
Cases of acute poisoning with pyrrolizidine alkaloids in foods are expected to only occur expected rarely in Germany and Europe. Health risks from a chronic exposure are the main priority for the risk assessment.

Serious, sometimes even fatal cases of poisoning have been observed in humans after an intake of high doses of 1,2-unsaturated PAs. For example, several thousand cases of endemically occurring poisonings have been documented in Afghanistan in recent decades. The cause of the poisonings 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, poisonings have also been linked to the consumption of certain herbs which are used in traditional Chinese medicine, and either contain 1,2-unsaturated PAs or are confused with or contaminated by plants containing PA. A case of poisoning was also reported to the BfR by attending physicians, in which an adult developed a severe liver function disorder after eating plant parts which contained 1,2-unsaturated PAs (medical disclosure of poisoning in accordance with §16e German Chemicals Act). PA-related poisonings are characterised in particular by veno-occlusive damage of the liver (and also of the lungs in rarer cases). Severe stomach pain, pain in the liver area, loss of appetite, fatigue, ascites, jaundice and liver enlargement are all examples of clinical symptoms of veno-occlusive liver damage which have been observed.

Severe cases of poisoning have occurred in livestock after the animals ate plants containing PAs. For example, the occurrence of liver cirrhosis has been observed in cattle who had consumed Alpine ragwort via hay and silage. Also, grazing of PA-containing *Senecio* species has led to seneciosis in horses, a condition 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 PAs?
The liver is the primary target organ for damage caused by 1,2-unsaturated PAs after chronic intake. 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 PAs 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.

Can the results from animal studies be transferred to humans?
While numerous case reports document the occurrence of the liver-damaging effects after short or medium-term intake of higher doses of 1,2 unsaturated PA in humans, there is a lack of epidemiological studies that could provide information about the cancer-causing potential.. However, it should be noted that in many cases it is difficult to prove such a correlation via epidemiological studies, since there can often be several decades between the intake of carcinogenic substances and the development of cancer. The available scientific data as a whole, however, indicates that the results from experiments on rodents for both liver-damaging and genotoxic-carcinogenic effects is transferrable to humans.

How are possible differences with regards to the carcinogenic potency of various 1,2-unsaturated PAs taken into account in the risk assessment?
In the case of 1,2-unsaturated PAs it is not the compounds but certain metabolites ('pyrrol metabolites') that are responsible for the toxic effects. Transformation into these reactive metabolites appears to be possible for all 1,2-unsaturated PAs. For some derivatives of the 1,2-

unsaturated PA this has already been proven experimentally. However, since the absorption and metabolisation of individual compounds may vary, depending on their respective structures, it can be assumed that this may have an influence on the potency of different derivatives of 1,2-unsaturated PAs. Differences of this kind have also been experimentally proven for various 1,2-unsaturated PAs. It has therefore been discussed if and how the different potencies of individual 1,2-unsaturated PAs and their *N*-oxides can be considered in more detail in future.

However, the BfR concludes that potency factors which were derived on the basis of currently available data and are proposed by various authors cannot yet be used to assess possible health risks of 1,2-unsaturated PAs. In particular, the potency factors suggested thus far still do not allow drawing any reliable conclusions on the carcinogenic potencies of different 1,2-unsaturated PAs after oral intake *in vivo*. For the assessment of the cancer risk, all 1,2-unsaturated PA are therefore currently combined into one group. This assessment is in line with the assessment of the European Food Safety Authority (EFSA), which also concluded that the current data still does not justify the use of potency factors for the risk assessment.

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

1. A major cause for the occurrence of 1,2-unsaturated PAs in foods is PA-producing plants, which grow in the cultivation areas of crop plants and contaminate food during harvesting. In Germany, for example, contaminations in lettuce caused by ragwort/groundsel have been found. Increased levels of 1,2-unsaturated PAs in wheat are known from Afghanistan, which were 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 PAs 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 PAs. 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 PAs can also find their way into the foodchain via contaminated feed given to livestock which then is transferred to the foods produced from the animals, such as milk and eggs. There are currently no indications, however, that levels which pose a health risk to consumers occur in foods of animal origin.
4. A further possibility is that foods originate from plants which themselves produce 1,2-unsaturated PAs. One such example is borage, also known as starflower. Borage, for example, is commonly used as a characteristic spice plant in ‘Frankfurt green sauce’. Food supplements may also be produced using plants, plant-parts, or plant extracts, which contain 1,2-unsaturated PAs themselves. For example, food supplements produced 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, levels of 1,2-unsaturated PAs in such food supplements can be very high. By contrast, no 1,2-unsaturated PAs have yet been detected in oil-based food supplements.

Can 1,2-unsaturated PAs easily be detected analytically?
The analysis of 1,2-unsaturated PAs 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 PAs using liquid chromatography, in combination with mass spectrometry. The results of several ring trials 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 PAs in children and adults?
For children aged 6 months to under 5 years, the intake of 1,2-unsaturated PAs 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 PAs 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 current estimation of PA intake from herbs/spices indicates, for example, that these may contribute significantly to both long-term and short-term exposure to 1,2-unsaturated PAs, despite low consumption quantities. Food supplements which exhibit high PA levels may also make a major contribution to the total intake of 1,2-unsaturated PAs via food as an additional exposure source for adults.

Are there maximum levels ('limit values') in the European Union for 1,2-unsaturated PAs 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.

At present, there are still no statutory 'limit values' within the EU in the form of binding maximum levels for the occurrence of 1,2-unsaturated PAs in foods. The European Commission and member states are currently discussing about setting maximum levels for certain foods such as tea and herbal tea, food supplements, pollen and pollen products, and certain herbs/spices.

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 pyrrolizidine alkaloids 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 ration between a suitable toxicological reference point and the human exposure to the substance. In the case of 1,2-unsaturated PAs, a so-called $BMDL_{10}$ of 237 µg/kg body weight and 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 PAs?
In the past, various measures have been taken by the food industry to reduce the levels of 1,2-unsaturated PAs in different food groups. For example, this has already led to a reduction in the levels in tea and herbal teas.

Nevertheless, the BfR recommends continuing efforts to reduce the levels of 1,2-unsaturated PAs in all food groups as far as it is technically feasible. This particularly applies to food groups such as herbs/spices, in which the current levels are still high.

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

- A basic prerequisite for the safety of plant-based foods is the care and attention taken 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 PAs 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 are laid down 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 PAs?
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. Special knowledge is required here to avoid plants that contain 1,2-unsaturated PAs, such as borage, coltsfoot and others.

- Consumers who take food supplements based on pollen or plants that produce 1,2-unsaturated PAs should be aware that these products may contain high concentrations of 1,2-unsaturated PAs. 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 PAs in levels that would pose a health risk to consumers.

BfR publications on this topic:

- https://www.bfr.bund.de/en/a-z_index/pyrrolizidine_alkaloids-192891.html

- BfR Opinion No 030/2016 of 28 September 2016. Pyrrolizidine alkaloids: Levels in foods should continue to be kept as low as possible https://www.bfr.bund.de/cm/349/pyrrolizidine-alkaloids-levels-in-foods-should-continue-to-be-kept-as-low-as-possible.pdf

- Press release 18/2013 of 15 July 2013. Levels of pyrrolizidine alkaloids in herbal teas and teas are too high https://www.bfr.bund.de/en/press_information/2013/18/levels_of_pyrrolizidine_alkaloids_in_herbal_teas_and_teas_are_too_high-187319.html

- BfR Opinion No. 018/2013 of 5 July 2013. Pyrrolizidine alkaloids in herbal teas and teas https://www.bfr.bund.de/cm/349/pyrrolizidine-alkaloids-in-herbal-teas-and-teas.pdf