Risiken erkennen – Gesundheit schützen

Frequently asked questions on pyrrolizidine alkaloids in foods

Updated BfR FAQ, 14 June 2018

High levels of 1,2-unsaturated pyrrolizidine alkaloids (PAs) have been detected in tea and herbal tea varieties in the course of various scientific projects. High levels of 1,2-unsaturated PAs can also occur in certain honeys, depending on their origin. In addition, the German Federal Institute for Risk Assessment (BfR) has assessed the health risks resulting from a lettuce mixture that was complained by a food control authority due to a contamination with *Senecio vulgaris* (ragwort, groundsel).

As 1,2-unsaturated PAs are undesired in foods and feeds due to their health-damaging potential, the BfR is of the opinion that above all food companies must take measures to lower 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 are secondary plant ingredients. It is assumed that certain plant species produce these substances in order to ward off predators. To date, more than 660 different compounds have been detected worldwide in over 350 types of plants. Overall, however, when chemotaxonomic considerations are taken into account, it is assumed that PAs occur in over 6,000 plant species. The pyrrolizidine alkaloid-containing plants are mostly members of the composite plants (asteraceae), forget-me-not or borage families (boraginaceae) as well as the legume family (fabaceae).

Examples of indigenous PA-producing plants are common ragwort, common groundsel and viper's bugloss. Chemically speaking, pyrrolizidine alkaloids are esters composed of a necine base and aliphatic mono- or dicarboxylic acids (necine acids).

Do foods containing pyrrolizidine alkaloids pose any health risks to consumers?
In animal studies, certain PAs show hepatoxic as well as carcinogenic and genotoxic effects. This applies to PAs with a 1,2-unsaturated necine base that is further esterified with at least one branched C5-carboxylic acid. Due to their health-damaging potential, 1,2-unsaturated pyrrolizidine alkaloids (1,2-unsaturated PAs) are undesired in foods and feeds.
The BfR has now drawn up an assessment of the possible health risks posed by 1,2-unsaturated PAs in foods on the basis of an estimation of the total intake using the latest data on PA levels in the relevant food groups. Based on this assessment, the levels of 1,2-unsaturated PAs in foods (herbal teas, rooibos tea, black and green tea and honey) could pose a health risk to children and adults if consumed over longer periods (chronic), but there is no acute health risk.

Are there known cases of poisoning with 1,2-unsaturated PAs?
Cases of poisoning are known with animals under such names as "walking disease", "dunziekte", "Winton disease", "Schweinsberger disease" and "Zdar disease". Liver cirrhosis occurred frequently among other effects in slaughtering cattle fed with hay and silage contaminated with alpine ragwort.

Cases of illness have also been described in the medical literature in humans who ingested high doses of 1,2-unsaturated PAs, but there are only a few well documented cases. In most cases, the symptoms affected the liver. In Pakistan, India and Afghanistan, people took ill after eating cereals that had been contaminated with seeds of the *Heliotropium* and *Crotalaria* species. In Jamaica, cases of poisoning were caused by so-called bush teas,

which contained parts of *Crotalaria* and ragwort. Within the scope of "Ärztliche Mitteilungen bei Vergiftungen" (Medical Notifications of intoxications), the BfR became aware of an adult who had eaten plant material containing 1,2-unsaturated PAs which caused a severe liver function disorder.

What chronic effects on health can 1,2-unsaturated PAs have?
The liver is the primary target organ for damage caused by 1,2-unsaturated PAs after chronic intake. However, other organs - the lungs in particular - can also be affected. Certain pyrrolizidine alkaloids proved to be genotoxic carcinogens in animal tests (long-term studies). Animal studies and experiments with cell models show that above all the metabolites of certain pyrrolizidine alkaloids are responsible for the hepatoxic and genotoxic-carcinogenic effects. Studies with liver cells of humans and rats also indicate that the occurrence of toxic substances during the metabolism of 1,2-unsaturated PAs is the same in the cells of rats and humans.

This is seen among other aspects as an indication that the results of studies with rats on carcinogenesis through 1,2-unsaturated PAs are also relevant to humans. In toxicological risk assessment, an extrapolation is usually made from results of this kind to the expected effect in humans. There are no epidemiological studies on PA-induced cancer in humans. The embryotoxic effect (toxic effect on the child in the womb) of certain pyrrolizidine alkaloids is also known from experiments with animals, but the data situation is unsatisfactory here.

How does the risk assessment take account of the possible differences with regard to the carcinogenic potential of 1,2-unsaturatedn PAs?
Based on chemical structure considerations, it is assumed that at least half of the known pyrrolizidine alkaloid compounds have a genotoxic-carcinogenic mode of action. As only a few of the 1,2-unsaturated PAs identified to date, however, have been thoroughly examined with regard to their genotoxic-carcinogenic effects, comparative statements on the carcinogenic effects of individual 1,2-unsaturated PAs are not possible at the present time.

The data that is currently available only enables to conclude on differences in acute toxicity but not on differences related to the carcinogenic effect of individual 1,2-unsaturated PAs. The assessment of the cancer risk therefore groups together all pyrrolizidine alkaloids with a double bond in 1,2 position (1,2-unsaturated PAs). This common structural characteristic basically enables “toxification” through oxidation to form dehydro pyrrolizidine, which possesses alkylating properties and is therefore potentially genotoxic and carcinogenic.

In line with internationally accepted guidelines such as those issued by EFSA or IARC, validated statements on the genotoxic-carcinogenic potential of an individual substance can only be made on the basis of existing animal studies on carcinogenicity and genotoxicity and/or robust epidemiological human data. The respective investigations must meet current scientific standards. However, suitable animal studies have only been conducted for riddelliine and lasiocarpine. Data for other 1,2-unsaturated PAs are generally only available in the form of results from in-vitro tests and in-vivo short-term tests, neither of which meet international assessment standards. This data does not permit any scientifically robust statements on the genotoxic-carcinogenic potential of the tested substances.

The risk of a genotoxic-carcinogenic effect of substances for which no suitable studies are available is assessed on the basis of known structure-effect relationships and allocation to a corresponding group or class. In the case of the group of 1,2-unsaturated PAs, for example, the risk assessment uses a “*read across”* method to make reference to known dose-effect relationships in the carcinogenicity studies of chemically related compounds. In addition,

substances for which there is inadequate toxicological proof but which possess structural characteristics that indicate a possible genotoxic-carcinogenic effect can be classified and assessed in line with the internationally accepted guidelines for the Threshold of Toxicological Concern (TTC).

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

1. 1,2-unsaturated PAs can find their way into food through contamination with PA-producing wild herbs in the cultivation areas of crop plants. Lettuce has been found in Germany that was contaminated with PA-producing ragwort/groundsel. Increased levels of contamination 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 varieties with 1,2-unsaturated PAs is also attributed to contamination of the raw materials which are harvested along with weeds in the cultivation areas that produce 1,2-unsaturated PAs.
2. Bee products such as honey and pollen can be contaminated with 1,2-unsaturated PAs originating from wild plants such as *Echium, Senecio* and *Borago* species from which the bees collect pollen. Raw honeys from certain countries of Central and South America have higher levels compared to those from several European countries.
3. 1,2-unsaturated PAs can find their way into food all along the food chain via contaminated feed given to livestock which then passes on to the foods produced from the animals, such as milk and eggs. There are currently no indications, however, that concentrations occur in foods of animal origin which pose a health risk to consumers.
4. The raw materials used in food production originate from plants which themselves produce 1,2-unsaturated PAs. Borage, also known as starflower, which is known to produce 1,2-unsaturated PAs, is used as one of the characteristic herbal ingredients of "Frankfurt Green Sauce". Food supplements may also be produced on the basis of plants and plant parts or extracts which produce 1,2-unsaturated PAs. Capsules are available, for example, which are made from hemp agrimony, a plant that produces 1,2-unsaturated PAs and that belongs to the *Compositae* family. The levels of 1,2-unsaturated PAs in some of these food supplements can be very high. No 1,2-unsaturated PAs have been found to date in oil-based food supplements.

Does the analytical detection of 1,2-unsaturated PAs pose any difficulties?
Due to their structural diversity, their low concentrations and their presence in a wide range of different foods, 1,2-unsaturated PAs pose special challenges in terms of their analysis. The BfR has developed special detection methods in recent years and validated them in ring trials. These methods can be used in food and feed monitoring programmes of the federal states and by the industry. As only a limited number of the occurring 1,2-unsaturated PAs are currently available as a reference standard, additional analytical methods were developed at the BfR so that the total concentration of 1,2-unsaturated PAs can be estimated.

Which foods contribute most to the intake of 1,2-unsaturated PAs in children and adults?
The intake of 1,2-unsaturated PAs by children aged 6 months to 5 years is mainly attributable to herbal teas (incl. rooibos tea), black tea and honey. Apart from certain food supplements, a similar pattern can be seen with adults. With adults, the contribution to total 1,2-unsaturated PA intake made by honey is lower, and that of green tea higher, than with

children. When their levels are high, food supplements as an additional source of exposure for adults can make a big contribution to total 1,2-unsaturated PA intake via food.

What is the situation with food supplements?
To answer this question, EFSA commissioned the testing of 191 food supplement samples. 1,2-unsaturated PAs were found in 60 percent of the samples, although in widely varying concentrations.

Food supplements containing plant material from PA-producing plants had the highest concentrations. The highest measured value was found in a capsule of a food supplement containing hemp agrimony (*Eupatorium cannabinum*) as one of its ingredients. Hemp agrimony is a plant that produces PAs. Other examples of PA-producing plants in food supplements are coltsfoot, comfrey, borage, lungwort, gromwell and butterbur. In the case of food supplements with high PA level, PA intake can be far higher than that via foods for daily consumption and can play a relevant role for the potential risk in the case of both short-term and long-term use. In individual cases, intake of such supplements may result in an exposure of 1,2-unsaturated PAs that is many times that via other foods.

The BfR and EFSA therefore both conclude that the consumption of certain food supplements based on PA-producing plants can result in the occurrence of acute toxic effects. Based on the available data, supplements containing St. John's wort were also found to be contaminated with PAs in virtually every tested sample. As St. John's wort is not itself a PA-producing plant, it is likely that the measured PAs are the result of contamination with other wild herbs. Food supplements based on bee products (pollen, beeswax, royal jelly) may also contain PAs.

Are there foods in which only very low amounts or no 1,2-unsaturated PAs at all were found?
Within the scope of a current EU project in which the BfR is involved, a very large quantity of data has been collected on levels of 1,2-unsaturated PAs in various foods, with very low levels of 1,2-unsaturated PAs or none at all being found in:

- Yoghurt, cheese (Gouda/Emmental, Brie/Camembert)
- Infant formula (milk powder 0-6 months), follow-on formula (milk powder 6-36 months)
- Beef, pork, poultry meat
- Beef liver, pork liver, chicken liver
- Eggs

Are there limit values for 1,2-unsaturated PAs in foods or regulations to minimise their concentration in foods?
There are still no legal limit values for 1,2-unsaturated PAs in foods and feeds, but the Codex Alimentarius Commission has prepared recommendations in a Code of Practice on "Management of the presence of PA-containing plants" and "Control of plant release and spread".

Within the European Union, the general recommendation applies that exposure to genotoxic 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. For this reason, the BfR recommends that total exposure to 1,2-unsaturated PAs from all foods should generally be kept as low as possible.

In the opinion of the BfR, which measures are necessary to reduce contaminations with 1,2-unsaturated PAs?
In order to minimise the potential health risk for people consuming honey as well as herbal and other teas in high quantities and especially for children, pregnant and breastfeeding women, various measures should be taken to reduce the 1,2-unsaturated PA levels of contaminated foods:

- One of the prerequisites for ensuring the safety of the foods in question is taking great care when cultivating and harvesting plants used to make herbal tea and tea as well as lettuces, leaf vegetables and herbs. For example , due to their conspicuousness, common groundsel types that may contain 1,2-unsaturated PAs are easy to spot in most cultures and can therefore be effectively controlled by suitable measures.
- Prior to marketing, food companies should continue to make sufficient checks in all affected food categories, especially batches of tea and herbal teas, and investigate the causes of high levels of 1,2-unsaturated PAs.
- Judicious selection of raw honeys which are used for the manufacture of mixed finished products can, for example, contribute to a reduction of 1,2-unsaturated PA levels in ready-to-eat honeys.
- The BfR supports consistent application of the recommendations made by the Codex Alimentarius Commission which are contained in the *Code of Practice* on the subjects *Management of the presence of PA-containing plants* and *Control of plant release and spread*.

What can consumers do in order to minimise the exposure to 1,2-unsaturated PAs?
The potential 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 be present in low quantities in foods can be prevented.

- Parents in particular are advised not to give their children only teas and herbal teas but also to offer them other drinks, such as water or fruit juice diluted with water. Expectant and nursing 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 lettuce, leaf vegetables and herbs, parts of plants which cannot be categorised 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 is viewed critically by 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 concentrations 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 020/2018 of 14 June 2018. Updated risk evaluation of levels of 1,2-unsaturated pyrrolizidine alkaloids (PA) in foods https://www.bfr.bund.de/cm/349/updated-risk-evaluation-of-levels-of-1-2-unsaturated-pyrrolizidine-alkaloids-pa-in-foods.pdf
- Press release 22/2018, 14 June 2018. Hazardous food supplements from natural sources https://www.bfr.bund.de/en/press_information/2018/22/hazardous_food_supplements_from_natural_sources-204965.html
- Stellungnahme Nr. 030/2016 des BfR vom 28. September 2016. Pyrrolizidinalkaloide: Gehalte in Lebensmitteln sollen nach wie vor so weit wie möglich gesenkt werden (German only). http://www.bfr.bund.de/cm/343/pyrrolizidinalkaloide-gehalte-in-lebensmitteln-sollennach-wie-vor-so-weit-wie-moeglich-gesenkt-werden.pdf
- Press release 18/2013, 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

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