



Undesirable in food

If pyrrolizidine alkaloids (PAs) enter the food chain, 1,2-unsaturated PAs in particular can harm human health. The BfR has been dealing for years with the question of what health risk 1,2-unsaturated PAs pose in foods. What is clear is that PA contamination in the food chain should be as low as possible.



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Undesired substances which find their way into the food chain can pose a health risk to consumers. An example for this kind is 1,2-unsaturated pyrrolizidine alkaloids (PAs), which are formed by several plants as protection against predators. They were detected initially in honey and other bee products and later in teas, herbal teas and spices, as well as in plant-based dietary supplements.

Toxic effects in humans and animals

In humans, sporadic cases of poisoning are known to have occurred after the pharmaceutical intake of herbal teas and products containing PAs. There are also reports of epidemic liver disease with fatalities in Pakistan, India, Afghanistan, Tajikistan and the former Soviet Union after the consumption of cereal contaminated with seeds of *Heliotropium* or *Crotalaria* species. In livestock farming, there are reports of the increased occurrence of liver cirrhosis in slaughtering cattle which had ingested alpine ragwort along with hay and silage. Seneciosis, a disease caused by PAs that is found together with liver degeneration, was also observed in horses.

The liver is the primary target organ for damage through 1,2-unsaturated PAs, although the lungs and other organs can also be affected. Acute hepatic veno-occlusive disease (HVOD) can occur in the liver or lungs, especially when higher doses are ingested. Developmental toxic effects have also been observed in animal tests involving higher doses of 1,2-unsaturated PAs. According to the latest available data from animal experiments, the carcinogenic effect of 1,2-unsaturated PAs is regarded as validated and a corresponding risk for humans is under consideration. Compounds that proved to be carcinogenic in animal experiments often showed a genotoxic effect in the corresponding mutagenicity tests.

How 1,2-unsaturated PAs can find their way into foods

According to the latest level of available knowledge, 1,2-unsaturated PAs can find their way into foods via several pathways. In Germany, contamination with PA-forming wild herbs has occurred above all in areas where crop plants are cultivated, e.g. lettuce with ragwort or groundsel. Increased contamination in cereals is known from Afghanistan. The contamination of tea and herbal tea varieties with PAs is also attributed to contamination with certain wild herbs in the areas under cultivation. In addition to this, bee products such as honey and pollen can be contaminated with PAs if the flow originates from certain wild plants. 1,2-unsaturated PAs can also find their way into milk, eggs and meat through contaminated feeds. Dietary supplements can also be produced on the basis of plants which form 1,2-unsaturated PAs by themselves.

Health risks through contaminated foods

The BfR made an assessment of the health risks of 1,2-unsaturated PAs in 2016. In the process, the contamination of all important food groups for which data on the occurrence of 1,2-unsaturated PAs is currently available was taken into account. The genotoxic-carcinogenic effect was used as the most sensitive endpoint in the assessment.



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Accordingly, intake of 1,2-unsaturated PAs in children aged six months to under five years was essentially attributable to herbal tea including rooibos tea, black tea and honey. Fruit tea, milk, eggs and meat contribute only a little towards overall intake of 1,2-unsaturated PAs. Apart from certain dietary supplements, the picture is similar with adults, except that the contribution of honey to the overall 1,2-unsaturated PA intake is smaller and that of green tea greater than with children. Dietary supplements containing high levels can contribute to the overall intake of 1,2-unsaturated PA via food as an additional exposure source. It is also possible that spices and herbs, as well as flours, constitute a relevant additional exposure source, but there is insufficient data come to a final conclusion.

Although high levels of 1,2-unsaturated PAs have been detected in certain foods for normal consumption in individual cases, the BfR believes that, based on the current data, acute health impairments are unlikely even if high amounts of these foods are consumed. As is internationally customary, the BfR used the MOE (margin of exposure) approach as the basis for estimating the potential risk of the genotoxic-carcinogenic effects. On the basis of animal studies, it is assumed here that an MOE value of 10,000 or higher for genotoxic carcinogens can be regarded as being of only slight concern from the point of view of public health, so that the priority for risk management measures is correspondingly low. No threshold dose can be assumed for genotoxic-carcinogenic substances below which undesired effects can no longer be expected. For this reason, the recommendation applies in the European Union that exposure to substances with genotoxic and carcinogenic effects should be minimised to the greatest reasonably possible extent in line with the so-called ALARA principle (as low as reasonably achievable). Even low intake quantities can be connected with increased health risks, especially with regular consumption.

The assessment of the genotoxic and carcinogenic risk was made by comparing overall intake via various teas, milk and honey in children and adults on the basis of various consumption scenarios with a BMDL 10 (Benchmark dose lower confidence limit 10 %) value of 73 micrograms per kilogram body weight and day with calculation of the MOE. The BMDL10 value is

an estimate of the lowest dose that causes a cancer incidence no greater than 10 percent in animal experiments with 95-percent certainty. All calculation approaches for children as well as the adult population produced MOE values well below 10,000. As an MOE should only be regarded as being of slight concern for public health from a value of at least 10,000 in the view of the EFSA scientific committee, the BfR recommends that overall exposure to PAs from all foods be kept as low as possible and that, under consideration of PA intake from all sources, the MOE should not be allowed to drop below 10,000. To achieve this, efforts should continue to further reduce PA levels in foods.

BfR research approaches

The BfR has been involved for several years with the problem of the contamination of foods with 1,2-unsaturated PAs and has been pursuing various research approaches in this regard. Due to their great structural variety and occurrence in many different foods, the analysis of 1,2-unsaturated PAs poses a special challenge. Over the last few years, the BfR has developed specific detection methods and validated them in ring trials. These methods are available at the BfR homepage and can be used in food and feed monitoring, for example.

In addition to the development of analytical methods, the molecular mechanisms of the toxicity of 1,2-unsaturated PAs are also being examined at the BfR. The main focus here is on the examination of the structure-dependent intake of 1,2-unsaturated PAs via the intestinal barrier. The results show that the toxic potency of the 1,2-unsaturated PAs can differ due to differences in structure-dependent transport



Plants which form pyrrolizidine alkaloids are to be found above all in the compositae (Asteraceae), „forget-me-nots“ or borage (Boraginaceae) and legume (Fabaceae) families.

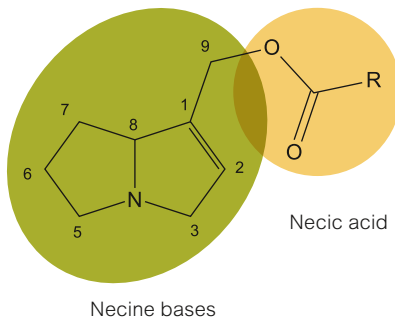




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The structure of PAs

From a chemical point of view, these are esters from a necine base and aliphatic mono or di-carbon acids (necic acids). Of particular importance from a toxicological point of view are pyrrolizidine alkaloids with a 1,2-unsaturated necine structure (1,2-unsaturated PAs). The 1,2-unsaturated necine structure as a common structural characteristic fundamentally permits toxicogenation through oxidation to dehydro pyrrolizidine, which is responsible for the genotoxic and carcinogenic effect of this substance group due to its alkylating properties.



via the intestinal barrier. The tested model substances also showed distinct structure-specific differences in metabolism in a cell culture model. Further examinations to the destruction of the sinusoidal endothelial cells through 1,2-unsaturated PAs should contribute towards understanding the mechanisms which lead to the veno-occlusive changes in the liver. Examinations of the metabolisation of nutrition-relevant pyrrolizidine alkaloids are also being conducted. The research projects are being sponsored by the German Research Foundation (DFG).

Recommendations to reduce PA levels

The BfR recommends that management measures should focus on the avoidance of the genotoxic-carcinogenic effects of the 1,2-unsaturated PAs as the most sensitive endpoint. Overall consumer intake of 1,2-unsaturated PAs should be as low as possible. To do so, PA levels in foods should be minimized as far as possible. This applies in particular to herbal teas, rooibos tea, black tea and green tea, as well as certain dietary supplements. Cultivation, harvesting and cleaning methods will have to be further improved to achieve this. The selection of the raw honeys can also contribute towards reducing levels of 1,2-unsaturated PAs in ready-to-eat honeys. In addition to this, monitoring by food companies in all affected food categories are still required.

Consumers can reduce the potential health risk of PAs by adopting a varied diet, thus avoiding general, slanted exposure to various potentially health-damaging substances. For children, expectant and nursing mothers in particular, the BfR recommends that the daily liquid requirement should not be met exclusively with herbal teas and tea.

When preparing salads, leaf vegetables and herbs, consumers should remove plant parts which they cannot identify as belonging to any known, edible plants.

Consumers of dietary supplements based on pollen or plants which form 1,2-unsaturated PAs should be aware that these products can contain 1,2-unsaturated PAs in higher concentrations. ■

More Information:
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