food supplements europe

Guidelines and recommendations to reduce the presence of pyrrolizidine alkaloids in food supplements

Addendum to the Food Supplements Europe Guidelines on Quality of Botanical Preparations: Recommendations for the Manufacturing of Botanical Preparations, including Extracts as Food Supplements

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Glossary

ALARA	As Low As Reasonably Achievable
BfR	Bundesinstitut für Risikobewertung
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EUROPAM	European Herb Growers Association
FSE	Food Supplements Europe
GACP	Good Agricultural and Collection Practice
GC-MS	Gas chromatography–mass spectrometry
HACCP	Hazard Analysis and Critical Control Points
LC-MS	Liquid chromatography–mass spectrometry
LC-MS/MS	Liquid chromatography–mass spectrometry/mass spectrometry
LOQ	Limit of Quantification
PA	Pyrrolizidine Alkaloids
SOP	Standard Operating Procedure
THIE	Tea & Herbal Infusions Europe

1. Introduction

Maximum levels for the presence of pyrrolizidine alkaloids (PA) have been set by the European Commission for a number of commodities, including food supplements. Regulation (EU) 2020/2040 establishes the following values for food supplements:[1]

– Food supplements containing herbal ingredients, including extracts: 400 µg/kg
(Herbal ingredients include extracts also from Camellia sinensis)

– Pollen based food supplements and pollen and pollen products: 500 µg/kg

These levels apply without prejudice to more restrictive national rules in certain Member States on the placing of the market of pyrrolizidine alkaloid containing plants.

The above levels apply to the final product as sold.

A transition period is foreseen until 1 July 2022 to enable operators to put measures in place to ensure these levels.

Food Supplements Europe has developed these guidelines to help all actors in the supply chain to prepare for these levels and to ensure that the accidental presence of pyrrolizidine alkaloids in food supplements is kept as low as technically possible.

This guideline will be kept updated.

2. Sources of PA

Pyrrolizidine alkaloids are ubiquitous in nature. Over 6000 plant species are known to contain them.

PA can be found in botanical preparations, whether used in general foodstuffs, tea, infusions or food supplements. PA are also found in bee products, such as honey and pollen. Some botanical crops are more vulnerable to the presence of PA than others.

Also food of animal origin can contain PA through ingestion of PA-producing plants by grazing animals or animal feed. The levels found are in the range of ng/kg.[2]

Since PA are genotoxic carcinogens,[3] their presence in the food chain must be avoided and kept as low as is reasonably achievable (ALARA).

The presence of PA in foods, including food supplements, can come from two sources:

– PA can be inherently present in certain plants or parts thereof (PA-producing plants). In the annex of this guidance, a number of plants that are known to contain PA are listed. **These plants should not be used in food supplements or when they are, the production process must be validated and adequately controlled to ensure that the residual PA content is below a specified limit in the final product.**

  In a number of Member States, strict limits for the presence of PA in such products are specified. These continue to apply.

  In case of insufficient quality control measures, the levels present can exceed the mg/kg range. This is considered a major risk for acute toxicity. Data presented by EFSA indicate that this is a real risk.[4]

– PA can also be present in a botanical preparation by accidental co-harvesting of PA-producing weeds (adventitious presence). The levels found are typically in the range of µg/kg. Although the contribution to daily PA exposure of food supplements accidentally containing PA is usually low, this is considered a potential concern for chronic toxicity.[2] Therefore, it is important to take appropriate measures to minimise contamination with PA.

– It should also be noted that not all PAs are equally toxic. Differences in toxic potencies are increasingly supported by different researchers and there is an opportunity for this in the future to be taken into account in risk assessment.[5]

This guidance will focus on the adventitious presence of PA in botanical ingredients. The presence of PA from contamination by weeds is rather unpredictable and can have a variety of causes. This guidance is therefore intended to raise awareness and increase the knowledge base of food supplements and botanical preparation manufacturers and their suppliers to help them address this issue to ensure compliance with legal provisions.

A number of general and product-specific guidance documents already exist that have contributed to the current guidelines that focus on food supplements in particular:

– In 2014, Codex Alimentarius adopted a code of practice for weed control to prevent and reduce pyrrolizidine alkaloid contamination in food and feed, aimed at providing good management practices for weed control of PA-producing plants to prevent and reduce the contamination of food and feed with PA.[6] This constitutes a global reference on the importance of PA exposure reduction and contains measures that should be implemented by operators world-wide.

– In 2018, Tea & Herbal Infusions Europe (THIE) published a Code of Practice to Prevent and Reduce Pyrrolizidine Alkaloid Contamination in Raw Materials for Tea and Herbal Infusions.[7]

– In 2019, the German food supplements association AK NEM published a Code of Practice that focuses on food supplements.[8] Recently, the German food federation Lebensmittelverband published a Code of Practice for the whole German food sector that incorporates a section on food supplements (and a reference to the AK NEM Code of Practice).[9]

– EUROPAM, the European Herb Growers Association and its members have developed several tools to help their members raise awareness and apply measures to reduce PA contamination in their crops.[10]

– Guidelines specifically addressing the manufacturing of medicinal products can also provide useful information, as the supply chain for botanicals used in medicinal products has many aspects in common.[11]

This guidance is a dynamic document that will be further refined and adapted to new findings.

3. General considerations and responsibilities

Since PA-producing plants are present in nature and can contaminate crops that are harvested or collected, the reduction of PA presence in foods and food supplements must be a **collective responsibility** and addressing the issue must be a collective exercise:

– All parties in the supply chain must work together and implement measures for the links of the chain under their responsibility.

  The higher up the chain, the more difficult it becomes to remove PA that have not been avoided in earlier steps.

– Weed control measures at farming level are key because PA-producing plants can spread to fields from road borders, grazing fields and cultivation grounds in the vicinity.

Responsibilities of food operators

The supply chain of botanicals and botanical ingredients is complex, with many small companies, often one-man businesses involved. Each food operator is responsible for the safety and legal compliance of the products under his control.

The final responsibility for compliance with the legal limits for PA lies with the operator responsible for the product as sold. This operator will therefore need to ensure that his product complies with the limits by a combination of measures, including raw material specifications and controls and measures implemented during sourcing, production and storage.

Operators upstream in the supply chain will have to implement the necessary measures and controls to ensure they meet the specifications set for their commodities (the botanicals as such) and derived ingredients (botanical preparations, extracts, etc). Suppliers will therefore need to implement appropriate measures and processes to ensure that their raw materials can be used in food supplements that meet the legal requirements.

For all operators, the first step in the process is to carry out a risk analysis of the operator's processes and product portfolio and identify appropriate measures to implement.

– For growers, brokers and suppliers of botanicals, this means understanding the risks of PA contamination for the specific crops they cultivate, collect or sell. This must be the basis for the identification of the most effective measures to be used in the context of establishing an integrated weed control system.

– For manufacturers of botanical extracts and preparations and final products this means identifying what risks are to be expected for the specific botanicals they are using. Based on available data on the different plant species that are known candidates for contamination of the specific crop used and monitoring data on the current level of PA contamination in their products, the manufacturers should identify the level of risk and define appropriate measures and test criteria for each of their products.

This 'hazard analysis' must be part of the integrated HACCP system (Hazard Analysis and Critical Control Points) in place. This assessment and the measures and criteria identified should be checked regularly and re-evaluated whenever necessary and, in every case, when changes in raw materials or product composition are implemented.

4. Measures at the stage of cultivation and harvesting (Grower)

Avoiding PA contamination is the most effective step to reduce PA exposure from food supplements.

This issue must be taken seriously by all links in the supply chain and collaboration from the stage of plant cultivation through to final product manufacturing is essential to move forward. Since measures to control PA in the fields take time because of the seasonal production process and the current limitations of agricultural-technical feasibility, **the limited transition period that the law foresees should be used to the maximum extent** to implement serious efforts to achieve compliance with the legal limits when the legislation enters into force.

Because of the non-homogenous nature of the contamination, its lack of predictability, the difficulties of recognising PA-producing weeds and the limitations of technical means to reduce PA contamination, reducing the presence of PA in consignments of botanicals and botanical preparations is hard and not to be underestimated.

This is of particular importance since the operators involved are mostly small businesses, farmers and smallholders, which do not always have access to information and resources. **Support from the extract and final product manufacturers is crucial for the supply chain to understand the requirements and overcome the challenges**. If not, suppliers may end up with unacceptable goods and manufacturers of extracts and final products may face shortage of compliant raw materials. Adapting practices to reduce the presence of PA will take time and cover several plant cycles.

Cultivated crops are easier to manage than collection of plants in the wild. In particular, wild collection often involves botanicals that are harvested by local smallholders, collected by local collectors, who gather truckload that are then sold in bulk to brokers and onwards to the processors. This will require much awareness raising and training, as a contamination in one of the harvest smallholders can render a whole truckload worthless.

Cultivation and harvesting

Accidental co-harvesting of PA-producing weeds lies at the basis of the presence of PA in the raw materials and hence in the processed products. Any cultivation environment should be considered as a real possibility for PA to enter the supply chain, because weed seeds may already be present in the soil, in seed mixes or may be carried over from neighbouring fields or roadside borders.

The presence of just a few weed plants can already result in levels that are detectable and exceed specifications. As an example, some weeds, such as Senecio spp. can contain high levels of PA. 6 plants with a PA load of 1,310 mg/kg on an area of one hectare that holds 60,000 plants will result in an amount of 0.1310 mg/kg of the dried harvested crop.

Managing weed infestation to reduce PA presence will be a combination of a number of measures including:

- Gathering knowledge and raising awareness
- Applying tiered risk characterisation to determine the risk of the cultivation environment
- Adherence to Good Agricultural and Collection Practices
- Implementing an integrated weed management

Gathering knowledge and raising awareness

Measures to limit contamination with PA-containing plants in the fields and during harvesting include a combination of early detection and prevention of contamination.

Knowledge to enable early detection and identification of these plants is essential. This requires appropriate (visual) tools to raise awareness and train farmers and collectors. Such training should be extended to the local population (including contractors and roadside maintenance staff) that are involved in maintenance and management of adjacent fields, pastures and road border sites.

Tools may consist of leaflets and website information with an overview and description of the most important PA-producing plants, expected in the respective cultivation or collection region, their ecology, and how to recognise them in their various states of development, like the examples presented in the annex of these guidelines and adapted to the nature of the business (e.g. smallholders vs. professional growers).

Actions to prevent contamination will be based on a **risk characterisation of the cultivation environment** and consist of the application of **Good Agricultural and Collection Practices (GACP)** and the implementation of an **integrated weed management plan**, using a combination of mechanical, chemical and biological methods and manual control.

Tiered risk characterisation

A tiered risk characterisation approach, as recommended by Tea and Herbal Infusion Europe, based on the Codex Alimentarius guidelines allows in a practical way to estimate the risk of a particular cultivation environment by assessing the following aspects:

- Are there PA-producing plants on arable fields, meadows, pastures, grasslands, road borders, etc in the proximity of the crop?
- Can the botanical species be identified?
- Can the level of infestation be estimated or quantified?
- Are local circumstances present that would promote the growth of certain PA-producing plants?
- Are the climatic conditions likely to promote the growth and spread of certain PA-producing plants?
- What is the soil type and its influence on the crop and PA-producing plants?
- What harvesting and post-harvest technology is available and/or feasible to address PA-weed infestation?

If there are no PA-producing weeds in the production fields so far, the physical distance to such plants in the neighboring environment is an important factor for avoiding contamination. There is a:

– **high risk** in case PA-producing plants are present and flowering or seeding within 50 meters.

  In this case immediate action should be taken to control the spread of PA-producing plants using appropriate control techniques.

– **medium risk** in case PA-producing plants are present within 50 to 100 meters.

  In this case, a control policy has to be established to ensure that when the situation changes from a medium to a high risk of spread, it is identified and dealt with in a timely manner using appropriate control techniques.

– **low risk** in case the land on which PA-producing plants are present is more than 100 meters away.

  In case of a low risk, no immediate action is required.

Based on this analysis the risk can be estimated and the nature of required measures identified.

GACP (Good Agricultural and Collection Practices)

The value of applying GACP is undisputed. Early detection and identification of species producing PA is fundamental for the implementation of appropriate measures. Careful application of GACP is the first step that can help minimise the risk of cross-contamination.

GACP is a quality system implemented by growers and collectors of (wild) plants to guarantee traceability, safety and quality. PA contamination can be prevented by dedicated procedures that should be developed by the responsible company of the herbal raw material. GACP guidelines foresee the implementation of Standard Operating Procedures (SOP). Therefore, GACP as a quality system is the basis for ensuring the quality of the plants harvested or collected in the wild. The proper development of the GACP and their constant application is crucial to avoid the presence of PA plants in herbal material.

The European Herb Growers Association (EUROPAM) has guidance documents that can be consulted, including the EUROPAM Good Agricultural and Wild Collection Practices (GACP) guidelines (Version 7.3) and the EUROPAM Practical GACP Implementation Guide (see www.europam.net).

Integrated weed management

The most effective way to control PA-producing plants is to apply a combination of agricultural, mechanical and chemical methods (integrated weed management).

This needs to be implemented after a thorough inspection of the cultivation grounds, as different PA-producing plants may react differently to a particular management measure. Also, not all practices are suitable for every type of land. The type of land (arable fields, pastures), soil, weather and climate conditions and areas bordering the crop are all elements to be taken into account.

Activities that can help contain the risk before harvesting can include:

- **Information and tools to assist in the recognition of PA-producing weeds** are essential. In the annex of this guideline, examples are given of PA-producing plants that can be used to identify PA weeds. Plant recognition applications can also be useful tools (e.g. plantnet.org).
- **Observation and inspection** of the fields to detect the presence of PA-producing weeds and identify fields free of the relevant weeds.
- **Knowledge** about the various weeds and their life cycle is also important e.g. to know what cultivation methods and species-specific actions to apply, what selective crop protection measures to apply or how to identify the best moment to remove PA-producing weeds and with what method.
- **Control of seeds and growing materials**. Depending on the plant species, seeds of the crop can be contaminated with seeds of PA-producing weeds. Actions to reduce this risk can include:
  - Harvesting of crop seeds after inspection of the field and intensive weed control to ensure that the fields are free of critical PA-producing weeds
  - Attention to cleanliness of harvesting and processing equipment
  - Controls of crop seeds purity
  - Buying certified crop seeds
- Applying **mechanical methods and tools** for intensive weed control such as using cultivator or finger weeder or hoeing, manual hand hoeing, camera assisted hoeing, flaming can reduce the presence of PA-producing plants.

  These practices are best applied before flowering of the PA-producing plants to prevent seed production and seed spread.

  The history of the soil is important since ploughing or other disturbance of the soil may lead to more germination by exposing buried seeds already present to sunlight. Seeds of some PA weeds, e.g., Echium spp. may remain germinable for decades in the soil.

  Since mechanical methods are not always effective in killing PA-producing plants and may even encourage them to re-shoot (e.g. tansy ragwort (*Jacobaea vulgaris*) and Paterson's curse (*Echium plantagineum*)), slashing or mowing may need to be executed on a very regular basis and be applied in combination with other control measures as part of the integrated weed management plan.

  Care must be taken to remove from the field or destroy any material that contains PA-producing weeds to avoid reintroduction by e.g. ploughing.

- Effective **manual control** requires removal of the root crown and all larger roots. Manual control may therefore have limited effectiveness, only for seedlings and young rosettes but not for bigger plants with deep roots.

  Hand weeding is useful for small infestations but not cost-effective for large ones, nor is it suitable for large areas of land. Nevertheless, hand weeding remains the most effective measure that can be implemented.

- **Appropriate disposal and waste management** of plants is important.

  Plants that have been removed by hand pulling or mechanical means must be handled and transported in a manner that prevents their spread. Closed boxes, bags or containers should be used and the plants should be destroyed, e.g. by burning.

  Weeds should be removed and destroyed immediately since some plants are able to form viable seeds very quickly and to avoid reintroduction in the soil by e.g. ploughing.

  PA-producing plants should not be transported or handled unnecessarily and only when stored in hermetically sealed bags or containers.

- **Crop rotation** leads to increased fertility of the soil, which in turn will reduce the impact of weeds. Weed suppression by suitable crops can also reduce the seeding and germination of weeds.

- **Mowing the field edge** to prevent spread and infestation of PA-producing plants and **weed-free buffer zones** between infested and un-infested lands also help to contain infestation.

- **Cleanliness** is a basic requirement. Any equipment, vehicles and machinery that gets in contact with the herbal products can spread weeds and seeds and should be cleaned to avoid contaminations. This is of particular importance if such equipment has been used in infested areas, as it can help spread seeds over wide distances.

- **Optimisation of harvesting technology** can help to avoid harvesting weeds with cultivated plants, e.g. by adjusting cutting height.

- **Application of herbicides**, authorised for the crop plant may be an effective way of controlling PA-producing plants in certain circumstances. It must be considered that herbicides may still have an effect on the crop itself and cannot be applied to organic production. Herbicides should preferably be used in combination with other control methods to increase the effectiveness of the weed management. In most countries only few herbicides are authorised for use on the crop plants typically of interest for botanical food supplements.

  The choice of herbicide depends on the specific PA-producing plant species and availability of appropriate authorised herbicides. It is better to use selective herbicides or limit the use of non-selective herbicides for spray topping the PA-producing plants. In case of established PA-producing perennial plants, it is better to use systemic herbicides. Systemic herbicides are absorbed either by roots or foliar parts of a plant and are then translocated within the plant system to tissues that may be remote from the point of application.

  The most effective time to spray herbicides is when the weed plants are actively growing and commencing flowering, i.e. in the spring before bloom when the weeds germinate and in the autumn applied to the new rosettes. Some PA-producing weeds, e.g. *Senecio vulgaris*, need to be controlled regularly as they may produce several generations throughout the whole cultivation period. PA-producing plants should not be sprayed when the plants are stressed either through lack of water, too much water, disease, insect or mechanical damage, as spray effectiveness will diminish.

- **Other methods** can also be used, although their efficacy is less clear:
  - Natural enemies of a plant, e.g. specific insects, may be used to control PA-producing plants. It may be an economical and effective method. However, efficacy must have been established and the natural enemy must not present an environmental problem itself. One example is the use of the ragwort flea beetle against Tansy ragwort.
  - Soil solarisation, soil sterilisation, etc. may only be effective in case of small infestations.

Post-harvest inspection of the botanical material during cleaning and drying can help to provide an indication of contamination. It is however impossible to detect every contamination and eliminate the non-desired plants at this stage.

It is recognised that there may be many practical difficulties for implementing all proposed measures, e.g. areas of land being too large, or inaccessibility of certain regions for agricultural machinery. Also, different measures may have different effectiveness.

Operators should gather information on these practical difficulties and levels of effectiveness to understand the challenges and find appropriate solutions and assist the growers and collectors in the practical application of the available tools.

Wild collection

Training of the collectors and purchasers of botanicals that are collected or harvested in the wild is crucial.

For botanicals that are collected in the wild, few measures can be applied to reduce the risk of PA presence. The most important risk is the harvesting of PA-producing weeds with the collected plants. The risk is lower with hand-picking as compared to mechanical collection.

The most important and mostly only measure that can help avoid co-harvesting of PA-producing weeds is awareness and knowledge about the type of weeds that can be expected and how to visually recognise these by training and providing usable tools.

In addition, inspection of the collected herbal material should also be performed by the company who purchases the fresh herbs from wild collectors in order to accept the material. The control should be carried out before the drying process. In case the wild collectors sell the herbs already dried, the inspection will be more difficult but, in any case, should still be performed carefully.

Producers should be aware of cross-contamination also for botanicals collected in the wild. PA-producing botanicals must be handled, transported and stored strictly separated. Such PA-producing botanicals include Symphytum, Borago, Pulmonaria, Tussilago, Petasites, Eupatorium, etc.

5. Measures at the stage of processing of the botanical preparation and final product

The legal limit applies to the final product, i.e. the food supplement as sold. The amount is expressed per unit of weight. Regulatory compliance monitoring by the authorities will consist of taking samples and analysing the content of PA of the final product. Authorities will usually not take samples of the raw materials for routine controls. Sampling and methods of analysis are currently under discussion by the Commission and the Member States.

The operator is obliged by law to notify national authorities whenever it considers or has reason to believe that a food which it has imported, produced, processed, manufactured or distributed is not in compliance with the food safety requirements and to immediately initiate procedures to withdraw the food in question from the market, where the food has left the immediate control of that initial food business operator. Exceeding the legal limit for the presence of PA in the final product is such a situation.

PA are not destroyed by standard processing methods. As soon as botanicals are processed into extracts, any PA contamination will be homogenised and possibly concentrated across the preparation. Since the legal limit applies to the final product, specifications for the raw materials used as ingredients (e.g. the botanical material or preparations/extracts) should be set to avoid ending up with a non-compliant final product. Analytical monitoring of PA content of such ingredients is in most cases the only measure to ensure compliance with specifications.

Limiting the risk of non-compliance during processing of botanical materials

Given the difficulty to predict PA contamination in the raw botanical materials by the available sampling methods, the resources needed, the costs for analysis involved and the impossibility to reduce PA contamination at the stage of processing, efforts should be focused on preventing contamination at the beginning of the supply chain. At the stage of the final product, it is in principle too late to intervene. At this stage, it will need to be verified that the measures put in place during raw material selection and manufacturing have resulted in an acceptable level of PA below the legal limit. Such verification should be applied by implementing a monitoring program for testing an appropriate number of samples.

The PA level in the raw materials is unpredictable and can vary between batches. Because of the heterogenous distribution, a spot contamination in part of the batch of raw materials can remain undetected. Processing smaller batches can help mitigate the risk.

Under Article 3 or Regulation 1881/2006, it is not permitted to mix foodstuffs complying with the maximum levels set out in the legislation with foodstuffs, which exceed these maximum levels. Foodstuffs that are subjected to sorting or other physical treatment to reduce contamination levels shall also not be mixed with foodstuffs intended for direct human consumption or with foodstuffs intended for use as a food ingredient.

The presence of PA is considered a hazard that needs to be covered by the operator's HACCP (Hazard Analysis and Critical Control Points) plan. Many aspects of the raw material, it's cultivation and processing will affect the risk of PA contamination and can therefore be considered in the action plan that is developed.

Since the legislation provides for a transition period, any operator processing botanicals and botanical ingredients should make good use of this time to ensure it can meet the limits, when they enter into force.

The first step is to carry out a screening of its product portfolio. This should enable operators to:

- **Identify the various raw materials of plant origin used**
  - The botanical used and knowledge about the risks associated with the specific botanical can give valuable insights into the presence of PA contamination (e.g. St John's wort is particularly prone to contamination with PA-producing plants).
  - The nature of the plant part used (e.g. aerial parts, fruits, wood or root parts). In general, PA are found in higher concentrations in seeds and flowering parts, with lower levels in leaves, stems and roots.
  - The growth cycle (annual or perennial).
  - The cultivation, harvest and processing conditions (mechanical harvesting, cleaning options).
  - Where available, audit reports of the grower's pre-harvest controls and GACP performance, or inspection reports of controls for acceptance of the fresh botanical material before the drying process.
  - Where available, batch-related documentation (e.g. field record) of the raw material supply chain. EUROPAM has developed a paper on necessary batch document information that can be consulted (see www.europam.net).
  - If plants are collected in the wild, the risk of accidental co-harvesting of PA-producing weeds could be higher, depending on the knowledge and experience of the collector.
- **Assess the likelihood or risk of PA presence**, based on the source material, its supply chain and the processing. This should permit assessment of the extent of risk for the different plants that are used.
- **Gather analytical results** of the presence of PA in the raw materials and/or in intermediate products that are identified as of relevance.
- **Gather analytical information on the final products** to assess the current level of compliance with the proposed PA limits. Since contamination may differ between batches, it is recommended to analyse several batches, produced with different lots of raw materials.

Based on the data and information collected, **a product-specific action plan should be developed**, including the setting of raw material specifications, action limits and a timeline for improvements.

To avoid analysis on final products, it is recommended to **implement testing** for the presence of PA, either on the raw materials or at a stage during the processing that can ensure a reliable result that can be representative for the content in the final product (homogeneous distribution of PA should be ensured). An appropriate risk-based testing strategy can be developed.

Measures that extract and final product manufacturers can undertake to minimise the risk of PA contaminated raw materials include the following:

- **Auditing of growers and collectors.**

  The presence of PA originates from accidental co-harvesting of PA-producing weeds. Since removing the weeds after harvesting based on visual inspection is virtually impossible, the performance of the grower or collector to avoid contamination is key.

  Auditing of growers on site and field inspection are tools to assess the performance of growers in applying pre-harvest controls. Pre-harvest controls can help identify undesirable weeds before harvesting. Particular attention should be given to adjacent field borders and non-cultivated areas, as these may constitute a continuous reservoir for the weed infestation.

- **Visual inspection of the incoming goods**

  Inspection of the botanical raw material can help to provide an indication of contamination, but is largely ineffective to detect every contamination.

- **Testing of incoming batches**

  Analytical testing is required to verify compliance with specifications.

  Detection of PA in dried botanicals is hampered by the inhomogeneous nature of the contamination. In order to achieve a representative test result, a suitable sampling is of the utmost importance. However, because the presence of PA-producing plants is a spot-contamination (to a certain extent comparable with the presence of certain mycotoxins), no universal reliable sampling methods are available. Rather, it has been found in practice that individual procedures based on experience are more suitable than general guidelines and should therefore be preferred.

  Sampling procedures should be developed based on risk assessment according the different raw botanical materials (e.g. part of the plant, size, kind of packaging) in order to obtain reliable results.

  Testing on processed materials that are sufficiently homogeneous (e.g. extracts) is often simpler and can avoid the need for further testing at subsequent stages of the production process.

  This also has the advantages of easier sampling, requiring less sample quantity or number of samples, and the analysis not being hampered by matrix effects of the final product. Knowing the PA content of individual preparations enables to calculate the content of combination products in which they are used as ingredients.

  Such analytical testing should be carried out on intermediate ingredients at an as early step in the production as possible where homogenisation is achieved (e.g. at the stage of the extract), to avoid being confronted with non-complying products higher up in the processing chain. If a sufficiently homogeneous distribution of PA can be assumed during later process steps, analytical testing on subsequent stages of production is not necessary. It would also cover all products in which the intermediate ingredient is used as it permits assessment of the level in the final product by simple calculation. Monitoring to confirm the effectiveness of the measures and criteria in place would suffice.

  Setting up a testing strategy requires a product-specific and risk-based approach depending on the specific botanical ingredients.

Where sufficient information is available about the risk of contamination and the measures applied by the suppliers along the supply chain, a risk-based approach to prioritisation can be developed and the extent of testing identified, e.g. routine testing in the case of high risk and little information about measures taken vs. periodic or skip testing in the case of low risk and confidence in the measures applied along the supply chain. Also, monitoring of performance to confirm the ability to consistently achieve levels below the legal limit may reduce the testing frequency.

– **Processing controls**

Depending on the product, processing can lead to reduced (dilution) or increased (concentration) amounts of PA in the resulting product. Once a preparation is homogenised (e.g. extract), the level found will be determining for the amount present in the final product.

In production environments in which PA-producing plants are also processed, HACCP measures should be in place to ensure that

- no contamination occurs with PA-producing plant parts during production.
- the risk of contamination of subsequent processing on the same production line is eliminated.

Contamination with known PA-producing plants should also be prevented during collection, harvesting, handling, transport, storage and packaging.

Deliberate use of PA-producing plants

Plants of the genera Symphytum, Borago, Buglossoides, Tussilago, Echium, Eupatorium, Petasites and others not mentioned here, contain PA by nature. Food supplements containing preparations obtained from these plants or parts thereof are at high risk for contamination with the plant parts containing PA and extremely high levels of PA may be present, resulting in acute toxicity.

When using plants that are known to contain PA as raw materials or ingredients in food supplements the risk of having high levels of PA present in the final product by inappropriate manufacturing and quality control is real.

These plants should therefore only be used provided the products comply with specified limits and necessary controls are foreseen in the company's HACCP system. Contamination of other productions needs to be avoided at all stages of the production flow.

In a number of Member States, low maximum limits for the presence of PA in such products are specified by law (in the range of 1-5 µg/kg) and restrictions as to the use of certain of these plants may also apply. These measures remain applicable.

6. Testing and analysis

What PA to test

Regulation (EU) 2020/2040 covers the following PA to be tested in food supplements:

- intermedine/lycopsamine, intermedine-N-oxide/lycopsamine-N-oxide,
- senecionine/senecivernine, senecionine-N-oxide/senecivernine-N-oxide,
- seneciphylline, seneciphylline-N-oxide,
- retrorsine, retrorsine-N-oxide,
- echimidine, echimidine-N-oxide,
- lasiocarpine, lasiocarpine-N-oxide,
- senkirkine
- europine, europine-N-oxide,
- heliotrine and heliotrine-N-oxide

Lower bound

The maximum level refers to the lowerbound sum of these 21 PA. This means that if a PA is detected below the limit of quantification (LOQ), the PA is considered to be absent (level is set at zero).

Co-elution

The following additional 14 PA are known to co-elute with one or more of the above identified 21 pyrrolizidine alkaloids, making use of certain currently used analytical methods:

- Indicine, echinatine, rinderine (possible co-elution with lycopsamine/intermedine)
- Indicine-N-oxide, echinatine-N-oxide, rinderine-N-oxide (possible co-elution with Lycopsamine-N-oxide/intermedine-N-oxide)
- Integerrimine (possible co-elution with senecivernine and senecionine)
- Integerrimine-N-oxide (possible co-elution with senecivernine-N-oxide and senecionine-N-oxide)
- Heliosupine (possible co-elution with echimidine)
- Heliosupine-N-oxide (possible co-elution with echimidine-N-oxide)
- Spartioidine (possible co-elution with seneciphylline)
- Spartioidine-N-oxide (possible co-elution with seneciphylline-N-oxide)
- Usaramine (possible co-elution with retrorsine)
- Usaramine-N-oxide (possible co-elution with retrorsine-N-oxide)

This means that these PA, when co-eluted are not to be individually and separately identified and quantified but are included in the sum of the PA present. In case these PA or some of them can be individually and separately identified with the used method of analysis, they have to be quantified and included in the sum separately.

Limit of quantification

The limit of quantification (LOQ) for each substance is at least 10 ppb (µg/kg).

Sampling and methods of analysis

One frequently used method is the one proposed by BfR, which is applied for medicinal products and measures 28 PA.[12]

Other validated LC-MS/MS, LC-MS, or GC-MS methods are also suitable, provided they are able to unambiguously identify the PA of relevance and allow quantification with sufficient sensitivity.

European Pharmacopeia is in the final stages of proposing its own method that may be used to control the limits under food law. This work is expected to be published in July 2021.

Further clarification on sampling and methods of analysis is currently under discussion by the Commission and the Member States.

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Annex: Examples of the main plants that produce pyrrolizidine alkaloids

The information presented in this annex is intended as help for suppliers and growers/collectors of plants and is not an exhaustive list of plants producing PA.

ACKNOWLEDGEMENT:

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Name species: *Anchusa arvensis* L.

Common name: small bugloss, buglossa minore, buglosse des champs, krummhals, miel de avispas.

Family: Boraginaceae

Alkaloids type: PA

Description: Erect plant 15-40 cm tall.

Stems: solitary or few, striate, strigosely hairy with unequal hairs; longer ones up to 2 mm long, arising from a swollen base. Hairs on leaves similar.

Leaves: the basal oblanceolate, obtuse, up to 10 cm long; cauline and upper leaves subsessile to sessile, lanceolate to ovate-lanceolate, entire to undulate or subdenticulate. Bracts leafy, but smaller. Pedicels up to 15 mm in fruit, hairy. Calyx 5-partite, accrescent in fruit; lobes linear-lanceolate.

Flowers: corolla blue, equalling or slightly exceeding the calyx.

Fruits: nutlets c. 3, mm long, transversely ovoid, rugulose. Basal ring thick, minutely rugulose.

Flowering Period: April-August.

Distribution: Europe, Africa, Minor Asia eastward to Tibet.

Habitat: commonly found as a weed from 900-3900 m.

Name species: *Borago officinalis* L.

Common name: common borage, borragine commune, bourrache officinale, gurkenkraut, borraga común.

Family: Boraginaceae

Alkaloids type: PA

Description: annual herb.

Stems: ascending to erect, usually branching above, 20-70 cm tall.

Leaves: the lower stalked, blades broadly elliptic or egg-shaped to oblanceolate, 5-15 cm long and 2-6 cm wide, the others reduced and shorter-stalked upwards, the uppermost often unstalked and clasping, alternate, entire or wavy-edged.

Flowers: inflorescence of several loose, terminal clusters with leafy bracts below; flower stalks spreading to drooping; corollas flat or somewhat backswept, star-shaped; petals bright blue, fused at base, spreading wide (to 2 cm across) to 5 sharp-pointed lobes, with 5 erect, notched, white, glabrous bulges at the throat; stamens purplish-brown, sticking out from the flower and forming a cone; fruiting calyces 1-1.5 cm long, densely bristly.

Fruits: nutlets 4, clustered together, oblong or egg-shaped, with a swollen budlike basal attachment surrounded by a thickened rim.

Flowering Period: June-August.

Distribution: Europe.

Habitat: dry to moist waste places in the steppe and lower montane zones.

Name species: *Cynoglossum officinale* L.

Common name: common hounds tongue, yao yong dao ti hu, lingua di cane, langue de chien.

Family: Boraginaceae

Alkaloids type: PA

Description: plant biennial, producing an unpleasant musky odor when bruised or crushed.

Stems: 30–60 cm long, densely pubescent with slender, relatively soft, sometimes somewhat woolly hairs, leafy to the tip.

Leaves: oblanceolate to narrowly elliptic, tapered to rounded at the base, sometimes slightly clasping the stem, angled or tapered to a sharply pointed tip, grading into the bracts, upper surface moderately roughened-pubescent with stiff hairs, the undersurface moderately to densely hairy with fine, softer hairs.

Flowers: inflorescences usually not paired, with leaflike bracts 1–5 cm long at all or most of the branch points. Calyces 6–10 mm long at fruiting, spreading or loosely cupped around the fruit, broadly elliptic to broadly ovate. Corollas purplish red.

Fruits: nutlets somewhat flattened along the dorsal surface, attachment point usually with a well-developed rim.

Flowering Period: May-July.

Distribution: Europe, Asia, introduced in U.S. and Canada.

Habitat: banks of streams and rivers; pastures, railroads, roadsides, disturbed areas.

Name species: *Echium vulgare* L.

Common name: common vipersbugloss, lan ji, viperina azzurra, vipérine commune.

Family: Boraginaceae

Alkaloids type: PA

Description: herbs biennial.

Stems: usually erect, to 1 m, usually much branched, spreading hirsute, densely short appressed pubescent.

Leaves: basal and lower stem leaves linear-lanceolate, ca. 12 × 1.4 cm, long strigose, base attenuate; upper stem leaves sessile, lanceolate, smaller. Inflorescences long, narrow, many flowered; bracts narrowly lanceolate, 4-15 mm.

Flowers: somewhat crowded. Calyx 5-parted to base, hirsute outside; lobes lanceolate-linear, ca. 6 mm, to 1 cm in fruit. Corolla blue-purple, oblique-campanulate, ca. 1.2 cm, short appressed pubescent outside; lobes unequal, upper lobe larger.

Fruits: nutlets ovoid, ca. 2.5 mm, tuberculate.

Flowering Period: July-October.

Distribution: Asia, Europe, North America.

Habitat: rocky areas; pastures, roadsides, waterways, gardens, disturbed sites and waste areas.

Name species: *Eupatorium cannabinum* L.

Common name: hemp agrimony, pei lan, canapa acquatica, eupatoire à feuilles de chanvre, eupatorio.

Family: Asteraceae

Alkaloids type: PA

Description: perennials, 30–150 cm.

Stems: from short rhizomes, single, branched distally, puberulent.

Leaves: opposite; subsessile or petiolate; blades palmately 3(–5)-lobed (at least larger proximal, lobes relatively broad), blades (or lobes) lanceolate to lance-ovate, 50–100 × 20–40 mm, margins serrate, apices rounded to acute, faces puberulent, gland-dotted.

Flowers: single flower-like, approx. 7 mm capitula, surrounded by involucral bracts. Capitula's ray-florets lacking; disc florets (5–6) reddish, tubular. Stamens 5. Pistil of 2 fused carpels. Involucre cylindrical, involucral bracts in 2 rows, round-tipped, with membranous margins, reddish. Capitula a corymbose inflorescence.

Fruits: 5-edged, greyish brown–black, approx. 3 mm long achene, tip toothed with unbranched hairs.

Flowering Period: July-September.

Distribution: Europe, Asia Minor, N Africa.

Habitat: Shady edge; bog garden, disturbed sites; 10–100 m.

Name species: *Heliotropium europaeum* L.

Common name: European heliotrope, tian jie cai, erba porraia, héliotrope commun.

Family: Boraginaceae

Alkaloids type: PA

Description: herbs annual, 20-50 cm tall.

Stems: erect or ascending, branched from base, strigose or hairy.

Leaves: petiole 1-4 cm; leaf blade elliptic to elliptic-ovate, 1.5-4 × 1-2.5 cm, abaxially gray-green and densely hirsute, adaxially green and sparsely hairy, base widely cuneate to rounded, apex obtuse to acute.

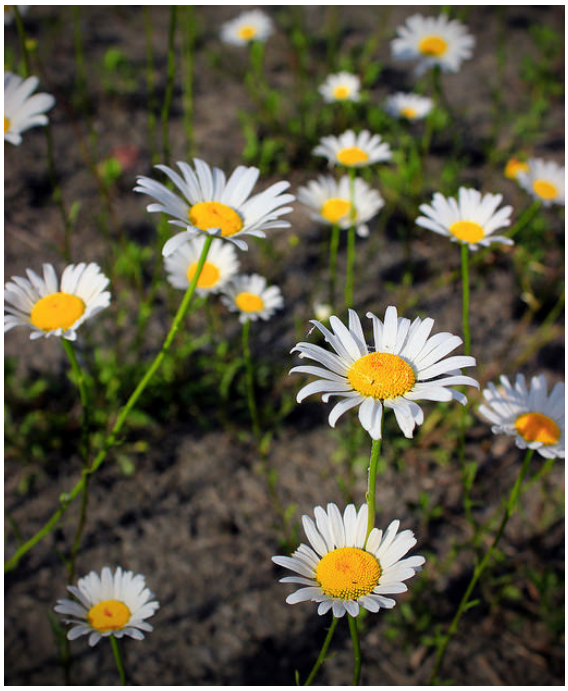
Flowers: cymes terminal and axillary, scorpioid, simple or dichotomously branched, 2-4 cm. Flowers sessile. Calyx lobes ovate to ovate-lanceolate, 2-3 × 1-1.5 mm, not enlarged in fruit, strigose. Corolla white, 4-5 mm, base 1.5-2 mm wide; throat slightly contracted; limb (2-)3-4 mm wide; lobes rounded, ca. 1.5 mm wide, short strigose outside, glabrous inside.

Fruits: 2.5-3 mm in diam.; mericarps ovate, ca. 2 mm, ± distinctly tuberculate, glabrous.

Flowering Period: June-November.

Distribution: S Europe, SW Asia, China, N Africa.

Habitat: gravelly deserts, river banks, valleys, cultivated fields; 0-800 m.



Name species: *Leucanthemum vulgare* Lam.

Common name: dog daisy, bin ju, margherita, grande marguerite, frühblühende margerite.

Family: Asteraceae

Alkaloids type: PA

Description: herbs, perennial, 15-80 cm tall.

Stems: erect, usually unbranched, tomentose, floccose, or glabrous.

Leaves: in the basal leaves petiole longer than blade; leaf blade narrowly elliptic, oblan- ceolate, obovate, or ovate, 3-8 × 1.5-2.5 cm, base cuneate-attenuate. Middle and lower stem leaves sessile; leaf blade narrowly elliptic to linear-elliptic, both surfaces glabrous, sometimes pinnatilobed below middle or near base, attenuate toward base, base auriculate- or subauriculate-semiamplexicaul. Distal stem leaves gradually smaller, sometimes pinnatisect.

Flowers: synflorescence a lax flat-topped cyme; capitula 1-5. Involucre coryliform, 1-2 cm in diam.; phyllaries in 3 or 4 rows, abaxially glabrous, scarious margin white or brown. Ray florets white; lamina 1-2.5 cm.

Fruits: achenes 2-3 mm, 10-ribbed, ribs projected into an apical rim. Pappus absent.

Flowering Period: May-October.

Distribution: native to Europe, introduced and naturalised elsewhere.

Habitat: widely cultivated as an ornamental, naturalised in grasslands.

Name species: *Lithospermum arvense* L.

Common name: corn gromwell, tian zi cao, erba-perla minore, gremil des champs.

Family: Boraginaceae

Alkaloids type: PA

Description: herbs annual. Roots with purple dye.

Stems: usually single, branched from base or only above, 15-30 cm tall, short strigose.

Leaves: blade oblanceolate to linear, 2-4 cm × 3-7 mm, short strigose, apex acute.

Flowers: cymes terminal, to 10 cm; bracts same shape as leaves but smaller. Flowers sparse, short pedicellate. Calyx lobes usually erect, linear, 4-5.5 mm, to 1.1 cm in fruit, short strigose on both sides, base becoming slightly hardened. Corolla white, sometimes blue or light blue, salverform; tube ca. 4 mm, sparsely pubescent outside; throat with 5 bands of hair extending to tube; limb ca. 1/2 as long as tube; lobes somewhat unequal, erect to slightly spreading, ovate or oblong, ca. 1.5 mm.

Fruits: nutlets gray-brown, triangular-ovoid, ca. 3 mm, finely tuberculate.

Flowering Period: April-August.

Distribution: Europe, SW Asia.

Habitat: hills, pastures, mountain slopes, margins of cultivated ground.

Name species: *Myosotis arvensis* (L.) Hill.

Common name: common forget-me-not, non-ti-scordar-di-me minore, myosotis des champs.

Family: Boraginaceae

Alkaloids type: PA

Description: annual or perennial herb, 15–40 cm high, erect.

Stems: branches with dense spreading hairs.

Leaves: moderately hairy, apex obtuse, margins flat; rosette leaves ovate, 2–10 cm long, 8–20 mm wide; cauline leaves oblong-lanceolate. Inflorescence axis with appressed antrorse hairs.

Flowers: on pedicels to c. 10 mm long; sepals 2.5–5 mm long, acute, connate in basal third to half, elongating with age, lower parts covered with hooked hairs; corolla 2–4 mm long, 3–5 mm diam., slightly exceeding the sepals, glabrous, bright blue with a yellow throat, tube longer than lobes; stamens and style included in corolla-tube, style shorter than stamens.

Fruits: mericarps c. 1.5 mm long, dark brown.

Flowering Period: April-July.

Distribution: Europe, NE Africa, Pakistan, Kashmir.

Habitat: ruderal in dry or moist places.

Name species: *Myosotis stricta* Link ex Roem. & Schult.

Common name: strict forget-me-not, small-flowered forget- me-not, non-ti-scordar-di-me a fiori piccolo, myosotis raide.

Family: Boraginaceae

Alkaloids type: PA

Description: annual herb up to 30 cm tall.

Stems: several to many, branched, covered with spreading unequal hairs up to 0.5 mm long.

Leaves: basal leaves 10-30 x 4-8 mm, oblong to obspathulate, covered on both surfaces with suberect hairs up to 1 mm long. Upper cauline leaves smaller, ovate-lanceolate; upper surface more densely hairy than lower ones.

Flowers: inflorescence up to 18 cm in fruit, lax. Pedicel up to 2.5 mm long in fruit, not reflexed. Calyx c. 2 mm half cleft in to linear-lanceolate lobes, basal part with slender suberect uncinate hairs, intermixed with short appressed hairs, those on the lobes appressed. Corolla blue, limb 2-3 mm broad, with spreading lobes.

Fruits: nutlets ± ovate, 1.4 mm long, smooth, shiny, light brown, areola minute.

Flowering Period: May-June.

Distribution: N Africa, Europe, Asia Minor, SW Asia.

Habitat: arid and sandy uncultivated lands.

Name species: *Petasites hybridus* (L.) G. Gaertn., B. Mey. & Scherb.

Common name: butterbur, pestilence wort, farfaraccio maggiore, gewöhnliche pestwurz, grand pétasite.

Family: Asteraceae

Alkaloids type: PA

Description: perennial herb, flowering stem develops in spring before leaves. Rhizomatous. Height: 15–40 cm, in fruit up to 100 cm.

Stems: at least in the beginning hairy at top, reddish brown–purple.

Leaves: alternate. Flowering stem leaves stalkless, scale-like, lanceolate, narrow-tipped, purple. Proper leaves long-stalked, blade kidney-shaped, up to 50–70 cm broad, cordate-based, angular, blunt-toothed, underside densely haired, top becoming glabrous, basal lobes round-tipped, basal gap often virtually closing.

Flowers: plant dioecious. Single flower-like capitula surrounded by involucral bracts. Capitula's ray-florets lacking; disc florets reddish, tubular. Involucre 5–8 mm long, involucral bracts usually purple, with entire tips, only hairy at base. Capitula 15–50, sturdy, in a racemose cluster.

Fruits: yellowish brown achene, tip with unbranched hairs.

Flowering Period: May-June.

Distribution: Europe, Asia, N America.

Habitat: usually found in wet, marshy ground, in damp forests, and adjacent to rivers or streams.

Name species: *Pulmonaria officinalis* L.

Common name: lungwort, polmonaria, pulmonaire officinale, lungenkraut.

Family: Boraginaceae

Alkaloids type: PA

Description: clump-forming, rhizomatous, evergreen perennial.

Stems: flowering stems originating among the leaf axils of rosettes, unbranched, 10–20 (30) cm tall with small clasping leaves.

Leaves: basal rosette leaves 16 x 10 cm, hispidulous, ovate, pointed at the apex, cordate at the base narrowing into winged stalks up to 15 cm; leaf lamina light green with clearly delineated pale green to silvery-white spots or blotches.

Flowers: inflorescence a terminal scorpioid cyme; flowers actinomorphic, 5–15 per stem. Corolla changing from red through purple to violet and finally blue, rarely white; petals 5, connate, not pubescent except for the hair ring at the entrance of the corolla tube. Calyx pubescent with five triangular teeth, swelling during fruit set.

Fruits: fruit a schizocarp of nutlets consisting of four nutlets with a single seed surrounded by a protecting hard pericarp. Nutlets 3.4 9 2.6 mm, ovoid and acute, dark brown to blackish at maturity.

Flowering Period: March-May.

Distribution: Europe.

Habitat: moist grasslands, damp woods and hedgerows.

Name species: *Senecio erucifolius* L.

Common name: hoary ragwort, senecione con foglie di ruchetta, séneçon à feuilles de roquette, raukenblättriges greiskraut.

Family: Asteraceae

Alkaloids type: PA

Description: perennial, 30–120 cm, herbage floccose-tomentose, unevenly glabrescent.

Stems: usually single, sometimes loosely clustered.

Leaves: ± evenly distributed (basal and proximal sometimes withering before flowering); petiolate (proximal) or sessile; blades ovoid or oblong to spatulate (usually pinnatifid to pinnatisect, lobes ± lanceolate to linear), bases tapered to ± truncate, ultimate margins (often revolute) dentate or entire.

Flowers: heads 20–60 in corymbiform arrays. Calyculi of 4–6(–10) bractlets (lengths to 1 / 2 phyllaries). Phyllaries ± 13, 5–7 mm, tips green or greenish. Ray florets ± 13; corolla laminae 12–15 mm.

Fruits: achenes are all shortly hairy and pappus is persisting.

Flowering Period: July-September.

Distribution: Europe, introduced in N America.

Habitat: grassland and disturbed habitats, including hay meadows and pastures, chalk and limestone downland, field-borders, railway banks, roadsides, waste places, shingle banks and fixed sand dunes.

Name species: *Senecio inaequidens* DC.

Common name: South African ragwort, senecione sudafricano, séneçon sud-africain, südafrikanisches greiskraut.

Family: Asteraceae

Alkaloids type: PA

Description: perennial herbaceous or woody shrub, up to 100 cm tall.

Stems: erect, leafy stems, numerously branched and glabrous, but sometimes sparsely hairy.

Leaves: alternate, usually sessile, occasionally petiolate, blade bright green, simple and slightly thickened. Basal l. sessile, linear to elliptic-lanceolate blades with acute apices; margins irregularly-toothed. Upper l. shortly petiolate, subsessile or sessile, occasionally pinnately-lobed.

Flowers: 80-100 terminal or axillary corymbose panicles. Radiate capitula with about 20 involucral bracts, bracts narrowly ovate, acute apices, ± glabrous, keeled. Calyculus bracts with acute apices, ± glabrous and dark tipped. Ray florets female, with bright yellow ligules.

Fruits: cypsela cylindrical, pubescent between ribs with a white pappus, readily detached.

Flowering Period: July-November.

Distribution: Africa, Europe, Central/S America, Australia.

Habitat: wastelands, fallows, railway tracks and roadsides, crops, burnt land and pastures, dunes and cliffs in littoral areas.

Name species: *Senecio jacobaea* L.

Common name: tansy ragwort, xin jiang qian li guang, senecione di San Giacomo, séneçon jacobée, Jakobs-geiskraut.

Family: Asteraceae

Alkaloids type: PA

Description: biennial or perennial herb. Rootstock short, erect. Height: 30–80 cm.

Stems: branched, deep-grooved, sparsely hairy, reddish brown.

Leaves: alternate, basal leaves and lower stem leaves short-stalked, upper stalkless, slightly amplexicaul. Basal leaves large, usually withered by flowering time. Blade 1–2 times pinnately lobed, underside usually sparsely hairy, lobes large-toothed, often roundish-tipped.

Flowers: flowers form 15–25 mm wide, single flower-like capitula surrounded by involucral bracts. Capitulum flowers yellow, ray-florets tongue-like; disk florets tubular, small. Capitula quite dense, borne in a corymbose cluster.

Fruits: round, ridged, glabrous–shortly haired, approx. 2 mm long achene with unbranched hairs on tip.

Flowering Period: July-September.

Distribution: native to Europe, N Africa and W Asia. Introduced into New Zealand, Australia, S Africa, NS America.

Habitat: roadsides, waste ground, railway embankments, ballast soil deposits, harbours, yards, meadows.

Name species: *Senecio nemorensis* L.

Common name: alpine ragwort, wood ragwort, lin yin qian li guang, senecione dei boschi, séneçon des forêts.

Family: Asteraceae

Alkaloids type: PA

Description: herb, perennial, rhizomatous.

Stems: solitary or sometimes several, erect, to 1 m tall, sparsely pubescent or subglabrous.

Leaves: basal and lower withered by anthesis; median stem leaves numerous, subsessile, lanceolate or oblong-lanceolate, papery, both surfaces sparsely puberulent or subglabrous, margin densely serrate, rarely coarsely dentate, apex acute-acuminate or acuminate; upper leaves somewhat smaller.

Flowers: capitula radiate, numerous, arranged in terminal and upper axillary compound corymbs; peduncles 1.5-3 cm, slender; bracteoles 3 or 4, linear, 5-10 mm, sparsely pubescent. Ray florets 8-10; lamina yellow, linear-oblong, 4-veined, 3-denticulate. Disk florets 15 or 16; corolla yellow, 8-9 mm wide, lobes ovate-triangular, ca. 1 mm, apically acute, papillose.

Fruits: achenes cylindric, 4-5 mm, glabrous. Pappus white, 7-8 mm.

Flowering Period: July-August.

Distribution: Europe, W Asia.

Habitat: open places in forests, meadows, streamsides.

Name species: *Senecio viscosus* L.

Common name: sticky groundsel, senecio vischioso, séneçon visqueux, klebriges greiskraut.

Family: Asteraceae

Alkaloids type: PA

Description: annual herb, height 20–50 cm.

Stems: branchless–branching from top, quite sturdy, densely tomentose and glandular-haired. With strong fragrance.

Leaves: alternate, lower short-stalked, upper stalkless, but not amplexicaul. Blade obovate, pinnately lobed, quite thick, covered in sticky glandular hairs, lobes toothed.

Flowers: single flower-like approx. 6–10 mm capitula surrounded by involucral bracts. Capitula flowers yellow, ray-florets tongue-like, often curled up; disc florets tubular, small. Involucre broadly funnel-shaped, involucral bracts 1 row, lanceolate, green, usually with black tips; outer bracts 3–8 at base of involucre, small, very narrow, usually entirely green. 5–25 capitula borne in a lax corymbose cluster.

Fruits: cylindrical, ridged, glabrous, brown, approx. 3–4 mm long achene, tip with unbranched hairs.

Flowering Period: July-September.

Distribution: Eurasia, introduced in N America.

Habitat: railways, roadsides, sand pits, wasteland, streets, fields, sandy shores, rocky outcrops, sea shores.

Name species: *Senecio vulgaris* L.

Common name: common groundsel, ou zhou qian li guang, senecio comune, séneçon vulgaire, gemeines geiskraut.

Family: Asteraceae

Alkaloids type: PA

Description: annual herb, height: 20–40 cm.

Stems: branchless–irregularly branching, bristly, usually quite swollen, usually sparsely haired–glabrous, underside often reddish. Lacking fragrance. Leaves: alternate, lower short-stalked, upper stalkless, amplexicaul. Blade pinnately lobed, thicket, usually shiny, sparsely haired–glabrous, lobes with toothed margins.

Flowers: single flower-like approx. 4–5 mm capitula surrounded by involucral bracts. Capitula flowers yellow, ray-florets usually lacking (occasionally tongue-like, soon curving downwards), disc florets tubular, small. Involucre cylindrical, involucral bracts 1 row, lanceolate, usually glabrous, with membranous margins, green, with black tips; outer bracts at base of involucre 8–10, small, triangularly lanceolate, with visibly black tips. Capitula borne in a dense, corymbose cluster.

Fruits: cylindrical, ridged, hairy along grooves, dark brown, 1.5–2 mm long achene, tip breaking off easily, with white unbranched hairs.

Flowering Period: June-October.

Distribution: widely distributed in the world.

Habitat: arable land, yards, gardens, flower beds, heaps of earth, wasteland, roadsides, sea-shores.

Name species: *Symphytum asperum* Lepech.

Common name: prickly comphrey, consolida ruvida, consoude rude, raue wallwurz.

Family: Boraginaceae

Alkaloids type: PA

Description: perennial herb, fleshy root, height: 60–200 cm.

Stems: roughly haired, especially at the top.

Leaves: alternate, narrow-stalked, shortly decurrent or usually not decurrent. Blade elliptic with a usually round or cordate base and entire margin.

Flowers: corolla bell-shaped (funnel-shaped), evenly expanding, 11–17 mm long, first pink, later sky blue, fused, 5-lobed. Lobes with rounded tips. Corolla mouth with 5 large, tongue-like scales. Calyx fused, 5-lobed, 2–5 mm long, clearly shorter than corolla funnel. Calyx lobes narrowly elliptic with rounded tips. Cymes in axils, single-branched or scorpioid.

Fruits: 4-parted schizocarp. Mericarps oblique, ridged, granular, matt.

Flowering Period: June-August.

Distribution: Europe, W Asia, N America.

Habitat: inhabited areas, parks, gardens, banks, coastline.

Name species: *Symphytum officinale* L.

Common name: comfrey, ju he cao, consolida maggiore, blackwort, beinwell, boneset.

Family: Boraginaceae

Alkaloids type: PA

Description: herbs forming tussocks, 30-90 cm tall, arcuate hispid, short strigose. Main roots purplish brown, stout.

Stems: erect or ascending, branched.

Leaves: basal long petiolate, lorate-lanceolate to ovate, 30-60 × 10-20 cm, apex acuminate; middle and upper stem leaves sessile, smaller, base decurrent.

Flowers: inflorescences many flowered. Calyx parted nearly to base; lobes lanceolate, apex acuminate. Corolla light purple, purple-red, or yellowish white, 1.4-1.5 cm; throat appendages ca. 4 mm, not exserted beyond limb; lobes triangular, apex revolute. Ovary usually sterile, occasionally only 1 mericarp develops in a few flowers.

Fruits: nutlets black, oblique ovoid or ovoid, 3-4 mm, smooth, shiny.

Flowering Period: May-October.

Distribution: Europe, N America, Asia. Cultivated also in Africa.

Habitat: damp, often shady localities, in meadows, woods, especially near streams and rivers.

Name species: *Symphytum × uplandicum Nyman* (hybrid between *S.asperum* and *S.officinale*)

Common name: Russian comfrey, consolida tedesca, consoude, futter-beinwell.

Family: Boraginaceae

Alkaloids type: PA

Description: perennial herb, height: 50–200 cm.

Stems: quite roughly haired.

Flowers: corolla bell-shaped (funnel–trumpet-shaped), upper part lightly budded, 12–18 mm long, red, blue or purple, on rare occasions almost white, fused, 5-lobed. Corolla lobes often slightly twisted. Corolla mouth with 5 large, triangular tongue-like scales. Calyx fused, 5-lobed, 5–7 mm long, shorter than corolla funnel, hairy. Corolla lobes usually pointed, on rare occasions with roundish tip. Cymes in axils, single-branched or scorpioid.

Leaves: alternate, stalked, shortly and narrowly decurrent. Blade ovate to elliptic with a rounded or cordate base and entire margins.

Fruits: 4-parted schizocarp. Mericarps oblique, wrinkled, granular, matt–slightly glossy.

Flowering Period: May-July.

Distribution: Europe, N America, Africa.

Habitat: inhabited areas, gardens, banks and coastline.

Name species: *Tussilago farfara* L.

Common name: Coltsfoot, kuan dong, tossilaggine, tussilage, huflattich, tusilago.

Family: Asteraceae

Alkaloids type: PA

Description: plants perennial. Rhizomes long creeping, subterranean, brown.

Stems: fruiting stems 5-10 cm tall, densely white lanate, with scale-shaped alternate purple-violet bracteate leaves.

Leaves: basal appearing after anthesis, long petiolate; petiole 5-15 cm, white lanate; blade orbicular-cordate, 3-12 × 3-14 cm, abaxially densely white tomentose, palmately reticulate veined, margin undulate, unequally toothed.

Flowers: capitula solitary, terminal, 2.5-3 cm in diam., nodding (or drooping) before and after anthesis. Involucres campanulate, 1.5-1.8 cm at fruiting; phyllaries 1- or 2-seriate, linear, white villous, glabrate, sometimes black glandular hairy, apically obtuse, often purple tinged. Ray florets female, many seriate, yellow, radiate. Disk florets few, functionally male; corolla tubular, 5-lobed. Fruits: achenes cylindric, 3-4 mm. Pappus white, 1-1.5 cm.

Flowering Period: April-June.

Distribution: N Africa, Asia, W Europe.

Habitat: Wet places, forest understories, valleys; 600-3400 m.

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