



Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations

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SCIENTIFIC OPINION

Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations¹

EFSA Scientific Committee^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Qualified Presumption of Safety (QPS) approach, initially developed for the assessment of microorganisms referred to EFSA and added to the food chain is equally applicable to the assessment of botanicals or botanical preparations. Using the principles to establish the suitability of a botanical preparation for QPS status, it has been possible to develop a structured assessment scheme that provides a practical method for assessing botanicals and botanical preparations for which an adequate body of knowledge exists and therefore without the need for further testing. Reiterative applications of the assessment scheme to related botanicals or different botanical preparations obtained from the same plant variety can allow a QPS status to be derived for specific groupings. However, the particularity of botanicals that may be presented in a wide variety of forms or whose morphology and chemical composition may be markedly affected by geographical and environmental factors, makes the possibility to establish QPS status at high taxonomic levels quite limited. Still, the above-mentioned structured approach for the assessment of botanicals and botanical preparations represents a considerable advancement in the development of a comprehensive, systematic and transparent methodology. The Scientific Committee recommends its use as an extension of the 2009 EFSA guidance for the safety assessment of botanicals and botanical preparations intended to be used in food supplements.

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KEY WORDS

safety assessment, botanicals, botanical preparations, presumption of safety, QPS, assessment scheme

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SUMMARY

The European Food Safety Authority (EFSA) asked the Scientific Committee to consider the applicability of the Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals / botanical preparations.

The QPS approach was initially developed for the assessment of microorganisms referred to EFSA and added to the food chain; it requires four elements: i) the ability to establish the identity of the group of organisms considered, ii) the need for a sufficient body of knowledge to define its nature, iii) the consideration of possible pathogenicity and whether a qualification could be introduced to exclude pathogenic strains, and iv) information on the intended use. A basic tenet of the QPS approach as originally conceived was that suitability for the QPS approach should be established at the highest taxonomic level possible.

The above-mentioned four elements are equally applicable to the QPS assessment of botanicals or botanical preparations. The particularity of botanicals that may be presented in a wide variety of forms or whose morphology and chemical composition may be markedly affected by geographical and environmental factors may introduce substantial compositional differences between preparations from the same plant species. As a result, the possibility to establish QPS status at high taxonomic levels will be quite limited.

Using these principles, it has been possible to develop a structured assessment applicable to botanicals and botanical preparations used in food which took as its starting point the existing Guidance document on the safety assessment of botanical supplements that also introduces the concept of presumption of safety in its first assessment level.

An exercise with examples showed that it is possible to create a list of plants for which a presumption of safety could be established. Data were collected for the purpose of this testing exercise only and are not the result of a structured data search. As such, the outcome of these QPS assessments should not be used elsewhere to support the safety of the botanicals and botanical preparations. For some botanicals, it may be possible to list individual species or groups of species from the same genus as is done for microorganisms, with the implication that use of the raw material or any extract of that material is presumed safe (subject to any qualifications). However, in contrast to the QPS list for microorganisms, the number of compounds of concern and their potential for differential extraction would mean that for other species only specific extracts could be included. As with microorganisms, exclusion from a QPS list would not imply a botanical or botanical preparation is unsafe, but that a case-by case assessment is required.

In addressing the mandate provided, the Committee also considered, within the overall context of the EFSA safety assessment strategy, the value of making the necessary pre-assessments and developing a list of botanicals and botanical preparations which could be presumed safe. This opinion shows that the pre-assessment of a very large number of botanicals and their preparations would be demanding of resources and time. Where use is likely to be restricted to sensory purposes, the QPS approach offers only limited advantages over the existing methodologies and may not be cost-effective in the short term. Relatively few botanical preparations have multiple uses, particularly when feed applications are not considered. Consequently there are only a limited number of occasions when the same material is subject to assessment under different regulations and by different panels. The few occasions when this does occur could be handled by normal processes within EFSA and would not justify establishing a QPS approach.

Finally, it should be underlined that the structured approach for the assessment of botanicals and botanical preparations described in Figure 1 represents a considerable advancement in the development of a comprehensive, systematic and transparent methodology. The Scientific Committee recommends its use as an extension of the 2009 EFSA guidance for the safety assessment of botanicals and botanical preparations intended to be used in food supplements. Recommendation is made that

EFSA keeps track of the safety evaluations of specific botanical preparations in conformity with the methodology described in the present paper, as a comparison of such individual assessments may lead, in the future, to the establishment/enlargement of a specific QPS status.

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BACKGROUND AS PROVIDED BY EFSA

The evaluation of the safety and efficacy of botanicals is currently covered by several European regulations depending on their application (see Appendix A). The existing regulations on feed additives and on traditional medicinal products allow for an integrated assessment of botanicals and botanical preparations (looking both at safety and efficacy aspects). For food use, the responsibility for safety is left to the manufacturers and Member States' Competent Authorities, while EFSA has been charged with the evaluation of the scientific substantiation of claimed beneficial effects.

Traditional use of botanicals and botanical preparations in a specific country has been the main basis for accepting the use of food supplements and/or traditional medicinal products and/or other products (e.g. teas and infusions).

At present, EFSA is required to evaluate botanicals / botanical preparations in the following areas:

- ANS: safety evaluation of botanicals / botanical preparations included in food supplements, safety evaluation of additives derived from botanical sources.
- CEF: safety evaluation of botanicals / botanical preparations from non-food sources for flavouring applications;
- FEEDAP: evaluation of safety and efficacy of around 300 botanicals with feed applications;
- NDA: evaluation of 1548 botanical claims on hold until the European Commission clarifies which approach to take;

The novel food regulation currently under revision (see Appendix A) implies that EFSA should have the capacity to quickly review the safety of botanicals which are “novel” for the European market, but have a history of safe use in their country of origin, and eventually raise safety objections that would call for a full safety assessment of the botanical.

A number of tools and guidance have already been developed by EFSA for assessing botanicals and botanical preparations (see section 2). However, a generic assessment system allowing for priority setting among the botanicals the Panels have to evaluate has not been established. Such a generic assessment system should be transparent, consistent across the EFSA Panels, take account of the whole body of knowledge on a particular botanical, including its history of safe use, in order to focus resources on botanicals or botanical preparations presenting greater risks or uncertainties.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The European Food Safety Authority requests the Scientific Committee to develop a generic assessment system allowing for priority setting among the botanicals the Panels have to evaluate. The system should be transparent, ensuring a consistent approach across the EFSA Panels, and take account of the whole body of knowledge on a particular botanical, including its history of safe use.

The Scientific Committee is requested to perform this mandate in two steps:

Develop a generic system for setting priorities among the botanicals to be assessed. For this purpose, the Scientific Committee is requested to consider:

The guidance for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA, 2009), which foresees that botanicals or botanical preparations for which an adequate body of knowledge exists could benefit from a “presumption of safety” without any need for further testing.

The applicability for botanical species of a Qualified Presumption of Safety (QPS) approach, similar to that developed for the assessment of selected microorganisms referred to EFSA and added to the food chain (EFSA, 2007).

The generic system will be tested with several examples taken from the Compendium of botanicals reported to contain inherent substances of possible concern for human health (EFSA Scientific Committee, 2012b). Should the botanical genus or species considered contain substance(s) of possible concern, the possibility to identify a dose under which such substance(s) could be concluded as being of no concern will be explored.

If deemed feasible and appropriate, define subsequent steps to develop a list of botanicals that are suitable for QPS status.

ASSESSMENT

1. INTRODUCTION

In 2007 EFSA formally introduced a novel system for the assessment of safety of microorganisms deliberately introduced into the food chain, based on a qualified presumption of safety (QPS) (EFSA, 2007). This was done to avoid unnecessary duplication of efforts within EFSA and to aid the focussing of activities on those organisms likely to present the greatest risks. All potential candidate microorganisms were initially assessed for their suitability for inclusion in the system, independent of any specific authorisation process. A number of species were identified for which no safety concerns were found and these formed the basis of the QPS list. All strains identified as belonging to the listed species are then presumed safe without any further safety assessment. For some other species, a proportion of strains were recognised to present a specific hazard such as the ability to elaborate a toxin. Provided that a proven method existed to identify the hazardous strains (the qualification) then the species was also included in the QPS list. In this case only those strains which meet the qualification and are shown to be free of the recognised hazard are presumed safe.

Four elements, referred to as pillars, were considered when establishing whether the QPS approach was suitable for a defined taxonomic group (e.g. genus or species) of microorganisms. First and foremost was the ability to establish identity. Without an unambiguous definition of the taxonomic unit under consideration it would not have been possible to connect to the remaining pillars of the assessment. The second pillar asked whether there was a sufficient body of knowledge based on published data and/or experience to exclude the likelihood of a hazard or, if identified, to define its nature. The third pillar was a consideration of possible pathogenicity and whether with existing knowledge a qualification could be introduced to be able to exclude pathogenic strains. The fourth and last pillar requires the assessment to take account of the intended use.

The task of pre-screening of specific strains for use in the food chain was made easier by the relatively few microbial taxonomic units involved and by the increasing availability of genomic data and bioinformatics analysis assisting in identifying potential hazards. This, coupled with a history of use, i.e. significant human consumption, ideally over a period of several generations by a diverse population covering a wide range of genetic backgrounds and age groups, and the absence of clinical indications, allowed conclusions on the safety for defined taxonomic groups, with a high degree of certainty regardless of use.

The QPS list of microorganisms is updated annually by the Panel on Biological Hazards. For strains belonging to taxonomic units excluded from the QPS approach, a case-by-case assessment is required.

Botanicals and botanical preparations

Recognising that concerns regarding the safety of botanical preparations used in food were widely raised in Member States, EFSA developed and published a guidance document that can be used for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA, 2009). At the same time EFSA, in conjunction with Member States, began to develop a Compendium of Botanicals listing those plants reported to contain toxic substances or components that might otherwise be of concern (EFSA Scientific Committee, 2012b).

The Guidance developed by EFSA describes a two tier approach in which the first level, described as Level A, is a safety assessment based on available knowledge. If the available data are considered inadequate to reach a sound conclusion on safety, Level B applies which foresees the generation of additional (toxicological) data. At Level A it may be concluded that a botanical or botanical preparation for which an adequate body of knowledge exists could benefit from a “presumption of safety” without any need for further testing. The knowledge needed to reach such a conclusion

resembles in some aspects that used to establish the suitability of microorganisms for the QPS approach. Both require a clear definition of the material being considered (first pillar in QPS for microorganisms) and familiarity including evidence of a history of safe use and the absence of any reported adverse effects (equivalent to second pillar in the QPS approach for microorganisms). However, it differs in one important respect from the approach taken with microorganisms. Conclusions on the safety of strains of microorganism included in the QPS are made without any restrictions on use or level of exposure. This is not the case with Level A which carries the restriction that “no significant increase of intake compared to historical levels is to be expected due to the intended levels of use in food supplements. This implies that not only use levels but also chemotypes of botanicals and the chemical compositions of the botanical preparations should be in line with those historically used. This approach can only be applied when intakes due to the intended levels of use are within the range of intake levels derived from the European Member States’ average diets or from studies on specific subgroups. It is recognized that the acceptability of such an approach relies mainly on the objective of not significantly increasing exposures beyond the levels linked to the “(safe) history of use”.

Application of QPS to botanicals and botanical preparations

Both the Guidance and the Compendium are tools intended to aid the assessment of botanicals and botanical preparations. They are not intended to produce a list of botanicals and botanical preparations that might be presumed safe. However, those botanical preparations which satisfy the criteria laid down in Level A of the EFSA guidance could form the basis for a list akin to that developed for microorganisms thought suitable for a QPS approach. A QPS approach applicable to selected botanicals could offer advantages for much the same reasons as led to its development for microorganisms (e.g. avoiding repetitive assessments, ensuring consistency of approach, directing focus to the more hazardous items).

The present opinion deals principally with botanicals and botanical preparations entering the food chain as food flavourings, food additives, as ingredients in food supplements, and as pesticides and biocides. A summary of the regulatory frameworks applicable to botanicals is provided in Appendix A. This opinion does not address the use of botanicals and botanical preparations in animal feed for two reasons. Firstly, whole plant material is considered a feed material and as such is excluded from any requirement for a safety assessment. Secondly, while plant extracts are considered feed additives and do require formal assessment, the considerable differences in absorption, distribution, metabolism and excretion found amongst livestock including fish makes it unlikely that a composite conclusion necessary for a QPS approach could be achieved.

In addressing the mandate provided, the Committee first considered the criteria to establish the suitability for a QPS approach to assess the safety of botanicals and how a structured judgement might be made. This took as its starting point the level A of the Guidance document for the safety assessment of botanicals, but where possible extended its scope beyond the constraint imposed by historical levels of exposure. A number of practical examples were then selected to test the applicability of the proposed methodology. Finally, the costs and benefits of making the necessary pre-assessments and developing a list of botanicals and botanical preparations which could be presumed safe were considered within the overall context of the EFSA safety assessment strategy.

2. EFSA GUIDANCE DOCUMENTS FOR THE SAFETY ASSESSMENT OF BOTANICALS AND BOTANICAL PREPARATIONS INTENDED FOR USE AS INGREDIENTS IN FOOD SUPPLEMENTS

The Scientific Committee focussed its work on botanicals and botanical preparations, including food supplements; the proposed approach for safety assessment is however applicable to other uses of botanicals and botanical preparations in the food and feed areas. The guidance of the Scientific Committee for the safety assessment of botanicals comprises:

- a list of technical, exposure and toxicological data needed to assess the safety of botanical ingredients.
- a two-steps approach for safety assessment.

The first level (level A) of the two-steps approach described in the SC Guidance (EFSA, 2009) makes use of the information on history of safe food use in Europe and the above-mentioned data directly available from the literature. Provided that no significant increase of intake compared to historical levels of intake of the botanical ingredient under consideration is expected due to the intended level of use in food supplements and whenever available data would demonstrate that exposure to known levels of the botanical ingredient has occurred in large population groups for many years without reported adverse effects, a presumption of safety may be applied to the considered preparation without any further request for testing. Botanicals reported to contain substances of concern (see EFSA Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food supplements (EFSA Scientific Committee, 2012b) could also be granted presumption of safety provided that intake remains below an acceptable health-based guidance value.

Exposure to the substance(s) of concern can also be considered in relation to the Threshold of Toxicological Concern (TTC) values. The EFSA Scientific Committee evaluated in 2012 the TTC approach as a tool for providing scientific advice about possible human health risks from low level exposures and its applicability to EFSA's work (EFSA Scientific Committee, 2012c). The opinion of the Scientific Committee identified however a number of (categories of) substances for which the TTC approach should not be used:

- High potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines).
- Inorganic substances
- Metals and organometallics
- Proteins
- Steroids
- Substances that are known or predicted to bioaccumulate
- Nanomaterials
- Radioactive substances
- Mixtures of substances containing unknown chemical structures

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel), in its guidance document on the scientific data required to be submitted for food additive evaluations (EFSA ANS Panel, 2012) refers to the SC guidance for the safety assessment of botanicals and botanical preparations (EFSA, 2009) for the assessment of additives derived from botanical sources. The ANS guidance gives the possibility for botanical food additives derived from conventional food sources with a long history of food use to benefit from a "presumption of safety" under certain circumstances when an adequate body of knowledge exists. The Panel took note of the requirement in the SC guidance on botanicals that "no significant increase of intake compared to historical levels is to be expected due to the intended levels of use" and further clarified that the definition of what is considered a significant increase, compared to historical levels, should be judged on a case-by-case

basis, as this implies that not only use levels but also chemotypes of botanicals and the chemical compositions of the botanical preparations should be in line with those historically used.

In cases where the anticipated intake of the botanical ingredient is significantly higher than the estimated historical intake level, or where no historical intake level could be identified, the SC guidance on botanicals requires that additional exposure data are provided and assessed under the second level (level B) of the assessment. Where it was not possible to conclude on presumption of safety at the level A assessment because of lack of data on some toxicological aspects, additional toxicological studies should be carried out and assessed under level B as well. Both the SC and the ANS guidance documents describe the type of studies needed in relation to the different toxicological endpoints (EFSA, 2009; EFSA ANS Panel, 2012).

For compounds that are genotoxic and carcinogenic, the Scientific Committee recommends the Margin of Exposure (MOE) approach (EFSA, 2005); the Scientific Committee clarifies in its opinion that substances which are both genotoxic and carcinogenic should not be deliberately added to foods but does not mention specifically how to address naturally occurring genotoxic and carcinogenic substances in botanicals or botanical preparations that have a long tradition of food use. In a follow-up statement published in 2012, The Scientific Committee clarified that the recommendation to use the MOE approach holds true also for impurities, such as unavoidable contaminants, residuals and by-products resulting from a production process (EFSA Scientific Committee, 2012a). In the case of impurities, breakdown and reaction products, metabolites, and low-level contaminants in food where an exposure assessment can be conducted, but on which there are few or no toxicological data, both the Scientific Committee and the ANS Panel suggested the use of the TTC approach (EFSA ANS Panel, 2012, EFSA Scientific Committee, 2012c).

Determining the suitability of a botanical or a botanical preparation for inclusion in a QPS list

It is recognised that there are significant differences in the assessment of botanicals compared to microorganisms which must be taken into account when assessing the suitability of a QPS approach to botanicals and botanical extracts. Relatively few microbial species are used by the food/feed industries compared to the many hundreds of botanical species. Similarly microorganisms are fed as live organisms not subject to further treatment while botanicals may be presented in a wide variety of forms (e.g. different parts and extracts) introducing substantial compositional differences between preparations from the same botanical species.

A basic tenet of the QPS approach as originally conceived was that suitability for the QPS approach should be established at the highest taxonomic level possible. For botanicals it is difficult to apply this principle. Many genera of plants contain hundreds of species/subspecies, few of which are fully characterised and consequently any pre-assessment may well be limited to a single species or even an extract or a specific part of a plant. In addition, morphology and chemical composition of plants may be markedly affected by geographical and environmental factors, not least from the selection of cultivars appropriate for a given region. All of these factors will influence the possibilities for grouping of botanicals and botanical preparations in a QPS approach and influence the decision on what materials can be included in the assessment.

Figure 1 presents a flow chart with a possible approach for the assessment of botanicals and/or botanical preparations, based on the data available, i.e. without requesting any testing. Given that the proposed approach is based on the data available without any further additional testing, it is basically in line with the so-called Level A assessment described in the SC guidance for the safety assessment of botanicals and botanical preparations (EFSA, 2009) and allows to eventually conclude on presumption of safety. The diagram includes various steps and should be applied in an iterative way considering upon finalising the QPS evaluation for one preparation whether other preparations or even preparations of related botanical species can be included. The next section describes in further details the various steps of the proposed approach for the QPS assessment of botanicals and/or botanical preparations.

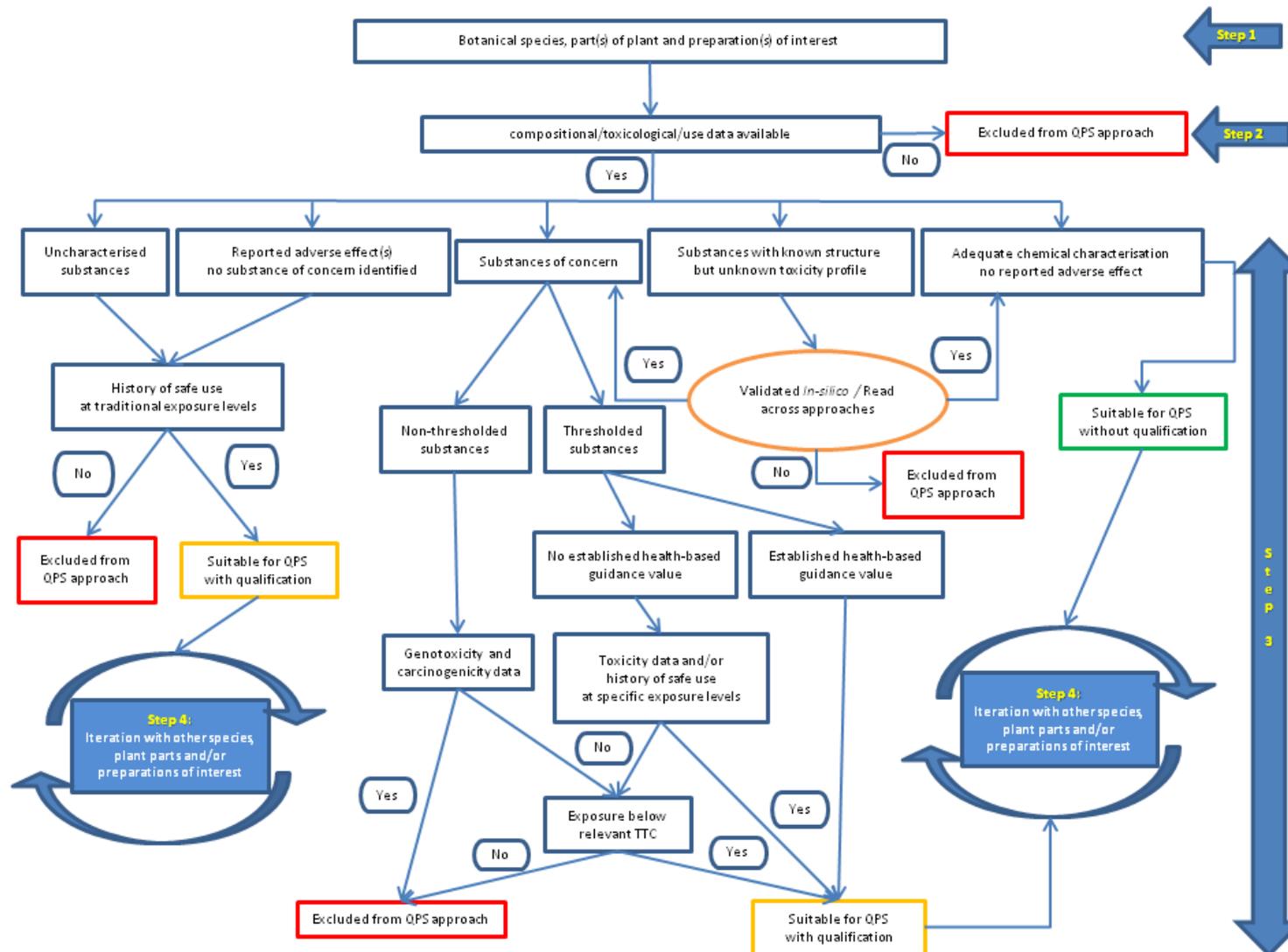


Figure 1: Flow diagram of the proposed methodology for QPS assessment of botanicals and botanical preparations.

Step 1: Defining the botanical species, part(s) of plant and preparation(s) of interest

In a first step, it has to be defined what plant species and what plant part(s) and type of preparation(s) are to be assessed. Given the large variation in composition that may exist between different subspecies/varieties of a botanical species, between a botanical grown under different environmental conditions, between different parts of the same botanical, and between preparations made using different manufacturing processes, -for example different extraction methods leading to different substances being extracted-, it is important to carefully define at the very beginning the botanical species and (part)s of the plant and preparations evaluated. Guidance on how to do this can be found in the previous EFSA opinion defining guidance on the safety assessment of botanical and botanical preparations intended for use as ingredients in food supplements (EFSA, 2009).

Step 2: *Evaluating the compositional / toxicological / use data*

In the second step, one should review the available data on the composition and toxicity of the botanical or botanical preparation as well as its constituents. Adequate compositional, use, and toxicological data should be collected in line with what has been described before in the Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA, 2009). The history of use should also be considered as part of the body of knowledge in line with the level A evaluation described in this Guidance. This knowledge can be especially of importance if the evaluation according to the decision tree in Figure 1 would lead to acceptance of only unrealistically low exposure levels compared to historical use levels. This process of data collection should define all biologically active substances described in the literature that have been identified in the botanical or botanical preparation, also including their actual levels. It is essential to define the percentage of the material that has been characterised, and what percentage of the preparation evaluated remains unidentified. In this process of identifying substances of concern other sources of data suggesting possible adverse effects and toxicity linked to the botanical or botanical preparation under evaluation must be included. Information on substances of concern can relate to isolated substances but can also be derived from data on the extract itself. If available, data on matrix and combination effects may also be taken into account when defining substances of possible concern.

Furthermore, the possibility of cross contamination from one part of the plant with compounds of concern to other parts of the same plant should also be considered. An example is the presence of morphine and codeine usually detected in *Papaver somniferum* L. (opium poppy) seed samples due to contamination with the latex or other parts of the plant (EFSA CONTAM Panel, 2011)

If compositional / toxicological / use data are available these data are evaluated in the next step.

Step 3: *Evaluating the compositional / toxicological data*

Once the available and relevant compositional and toxicological data are defined this may result in five possible situations, reflected in Figure 1 (from right to left):

The chemical characteristics of the botanical or botanical preparation are adequately defined and no adverse effects are reported. In such situations presumption of safety may be assigned without the need to introduce any qualifications, such as defining the exposure limit for which the QPS status holds.

The botanical or botanical preparation contains substances with known structures but unknown toxicity profiles. In such situations one may investigate whether based on validated *in silico* or read-

across approaches adequate predictions can be generated without the need for further toxicological testing. If the *in silico* and/or read-across approaches do not give results suitable for subsequent risk assessment, the botanical or botanical preparation will require further toxicological testing and has to be excluded from the QPS approach until additional data have been provided. In case *in silico* or read-across methods can generate information on the substances with known structures but unknown toxicity profiles, the botanical preparation may be granted QPS status without qualification, provided chemical characterisation was adequate and there were no reports on adverse effects. In the case where *in silico* and read-across methods identified possible toxicity, the substance becomes a “substance of concern” and the preparation shall then be evaluated for possible QPS status following the approach described in the next bullet point. The *in silico* predictive models are essentially based on structure-activity relationship (SAR), quantitative structure-activity relationship (QSAR), or a read-across between a group of analogous compounds that have structural and/or functional similarities to the untested compound. A wide range of methods and tools is already available for *in silico* toxicological profiling of a wide range of chemical substances, and can also be useful for compounds from botanical or other natural sources. Expert systems, on the other hand, can combine different *in silico* approaches to predict toxicity of a chemical substance from its structure. These may comprise decision-trees based on rules, structural alerts, and/or nested (Q)SARs. The (Q)SAR models are only reliable when they are tested rigorously for robustness and predictivity and their ‘applicability domain’ is clearly defined. In regard to *in silico* estimation of toxicity of botanicals, the issue remains of how to assess such a mixture where more than one main components are of unknown toxicological significance. Until recently (Q)SAR and other *in silico* methods have not been considered useful tools for such assessments, but work is ongoing to allow for the read-across assessment of mixtures. Finally it should be underlined that the use of the (Q)SAR models, expert systems, read-across tools, etc would need a clearly identified chemical structure, which may be a limiting factor for the application of the approach to botanicals and botanical preparations for which only limited analytical data are often available.

The botanical or botanical preparation contains substance(s) of concern. When the substance is acting by a thresholded mode of action (MOA), the exposure resulting from the use of the botanical or botanical preparation must be evaluated against established health based guidance values, using a Margin of Safety (MOS) approach, or compared to available toxicity data or data on the history of safe use at specific exposure levels to define a safe level of intake. This safe level of intake can be taken as the basis to define QPS with a qualification defining the exposure limit for which the QPS status holds. If for the substance(s) of concern with a thresholded MOA, no health based guidance values or toxicity data enabling definition of a safe level of intake are available, one may apply the TTC concept (EFSA Scientific Committee, 2012c) to define an exposure qualification to be linked to the QPS status. Application of the TTC approach requires that the chemical structure of the substance(s) with unknown toxicity profile is defined. It is noted that, with the exception of flavour use, application of the TTC approach may often result in exposure qualifications for the QPS status that are far below the proposed uses and use levels of the botanicals or botanical preparation of interest finally resulting in excluding the relevant botanicals or botanical preparations from the QPS approach. If a safe level of intake for substance(s) of concern cannot be established, the botanical or botanical preparation cannot be assigned a QPS status. This is the case for substance(s) acting by a non-thresholded MOA, e.g. genotoxic and carcinogenic substances. The Margin of Exposure (MOE) approach (EFSA, 2005; EFSA Scientific Committee, 2012a) may be applied to define their level of concern but, given the recommendation of the Scientific Committee to not introduce in the food chain substances that are known to be genotoxic and carcinogenic (EFSA, 2005), these substances will be excluded from the QPS approach and therefore subject to a case-by-case assessment.

The botanical or botanical preparation has been linked to adverse effects but compounds of concern are not identified. In this situation one may base the QPS decision on data available on the history of safe use at traditional exposure levels, provided that the adverse effects reported occurred at non-traditional levels of use. If such data are not available, the botanical or botanical preparation should be excluded from the QPS approach. If data on the history of safe use at defined traditional exposure

levels are available, these traditional exposure levels can form the basis to define a QPS status with qualifications.

The final possible outcome may be that the botanical or botanical preparation contains a fraction of uncharacterised substances. This may often be the case since full chemical characterisation of a botanical or botanical preparation may often not be available. In such situations one may also base the QPS decision on the available data on history of safe use at traditional exposure levels. If such data are not available the botanical or botanical preparation should be excluded from the QPS approach. If data on the history of safe use at defined traditional exposure levels are available these traditional exposure levels can form the basis to define a QPS status with qualifications.

Products commonly eaten are presumed safe unless a significant risk has been identified. Absence of evidence of toxicity, however, is not necessarily evidence of absence of toxicity under the proposed conditions of usage (e.g. long-term use of herbal preparations). Therefore, when considering history of use and accumulating the body of knowledge describing the safety profile of a botanical preparation, a number of important factors should be considered where available: the period over which the traditional preparation has been consumed, the way it has been prepared and used and at what intake levels, known limitations and restrictions for sensitive populations, its composition, the results of animal studies, observations from human exposure and clinical reports (Constable et al. 2007).

Step 4: *Repeating the steps in an iterative process*

When positive conclusions on safety have been reached, either with qualifications or not, after evaluating a specific botanical preparation, it may be relevant to repeat the process in an iterative way to other species / plant parts/ preparations. This step 4 should therefore include a consideration about whether there are similar preparations from other subspecies/varieties/ species for which the assessment could be relevant and if the safety evaluation could be extended to other preparations from other species/varieties, thus extending the number of botanical preparations for which the QPS status would hold. Considering which other botanical species/varieties and/or preparations could be covered by the specific safety evaluation can best be done starting from the chemical compositions. In fact, if the chemical compositions obtained from different species/varieties/plant parts or preparations are similar it would be reasonable to extend the safety evaluation obtained initially. This might be possible even if some quantitative differences would be detected among the chemical compositions. In addition, the described safety assessment procedure could be applied in an iterative manner, starting with evaluation of one botanical and/or botanical preparation and subsequently considering the feasibility of expanding the conclusion(s) obtained to other species/varieties or botanical preparations. The grouping should preferably include plants relevant for food consumption and with a history of safe use. It is also important that the botanical species and preparations evaluated are chosen as broad as possible, although it is acknowledged that evaluation at the species level may often be hampered by the wide variability between related varieties within a species. In some cases QPS may be granted for a single preparation and no extension or iteration is possible hampering the suitability of the QPS approach at higher taxonomic levels.

3. TESTING THE SUITABILITY OF THE QPS APPROACH FOR BOTANICALS

The present section aims at testing the proposed approach for the QPS assessment of botanicals and botanical preparations with selected case studies. Data were collected for the purpose of this testing exercise only and are not the result of a structured data search. The outcome of this assessment should not be used elsewhere to support the safety of the botanicals and botanical preparations. Further details on the data considered and how the flow diagram (Figure 1) was used for the QPS assessment of the selected case studies can be found in Appendix B.

There are species and genera for which compositional data exist but for which the Compendium and other sources do not identify substances of concern. One example is the fruit (hips) and petals of *Rosa canina* and related species. There is a long history of human consumption and more recently hips in concentrated form have been used in food supplements with a variety of claimed benefits, not all related to the recognised high concentration of vitamin C. Since a search revealed no reported adverse effects, apart from digestive tract and mouth irritation resulting from the ingestion of the hair-like layer under the flesh of the hips, the structured assessment in Figure 1 would lead to the outcome that *R. canina* fruit and petal could be included in a QPS list without qualifications. Repeating the process for other *Rosa* species would add to the list.

Citrus also represents a genus for which extensive data on the composition of the fruit, peel, and essential oils derived from them can be found for some species. However, unlike *Rosa* spp. the Compendium and the open literature identify the presence of linear furocoumarins with recognised phototoxic effects as compounds of concern in essential oils of many *Citrus* spp. Because of the use of such compounds in the oral treatment of skin diseases, their toxicokinetics are known and long and short term toxicity studies exist. From Figure 1 it is probable that sufficient toxicity data exist which would allow many *Citrus* spp to be included in a QPS list with a qualification relating to the linear furocoumarin content. However for a few *Citrus* spp., notably *Citrus aurantium*, a further compound of concern has been identified; animal experimental studies and human data have shown that *Citrus aurantium* extracts can induce cardiovascular effects, ascribed to the presence of (-)-synephrine. Following Figure 1, (-)-synephrine is a thresholded substance for which no health-based guidance value was set. Since the existing toxicity data are insufficient to derive such a value, use of extracts of *Citrus aurantium* in food supplements would have to be restricted to levels where no significant increase of (-)-synephrine exposure compared to historical intake levels with traditional foods is to be expected. Thus *Citrus* exemplifies a genus for which different conclusions with regard to a QPS approach would be reached for different species.

Rosmarinus officinalis was selected because it represents a case where, although only a single species is generally used, many different preparations and extracts are used each with substantially different compositions. Unusually, non-aqueous extracts of rosemary leaves have already been assessed for safety by EFSA. This resulted in a QPS-like conclusion that non-aqueous extracts were safe for use in food provided a qualification that the carnosic acid plus carnosol content remained within specified limits was observed. Although the Compendium identifies only monoterpenes as compounds of concern, which are poorly soluble in water, aqueous extracts contain very high concentration of rosmarinic acid. The very limited available toxicity data for rosmarinic acid do not suggest a hazard but are insufficient to derive a threshold value. A QSAR approach may solve this issue and could allow a QPS listing without qualification. The essential oil of Rosemary has a high monoterpene content, notably camphor. The traditional use of rosemary for abortion, coupled with preliminary evidence showing embryotoxic effects of the oil is cause for concern. Additionally, the oil provokes genotoxic and mutagenic effects when administered orally. Consequently the essential oil is not suitable for food use. Thus assessment of rosemary and its various extracts show that a composite conclusion on the species is not possible and that any QPS listing could apply only to specific extracts.

Foeniculum vulgare (fennel) and *Ocimum tenuiflorum* (holy basil) present similar issues as both contain the genotoxic and carcinogenic agent estragole. Given the recommendation of the Scientific Committee to not introduce in the food chain substances that are known to be genotoxic and carcinogenic (EFSA, 2005), *Foeniculum vulgare* and *Ocimum tenuiflorum* are excluded from the QPS approach. For risk management purposes, it may be of interest to assess preparations of these species on a case-by-case basis, using the carcinogenicity data for estragole from which a BMDL₁₀ could be derived and for which it is therefore possible to apply the MOE approach. The fact that some preparations e.g. essential oils of *Foeniculum vulgare* and *Ocimum tenuiflorum* species will show higher levels of estragole than the levels extracted into (traditional) water based preparations should then be taken into account. For preparations other than the essential oil of *Ocimum tenuiflorum*, there is an additional concern related to reproductive effects. Since the chemical(s) of concern for the

reproductive effects have not been identified and as the compositional data are limited, this is an additional argument to exclude extracts of *O. tenuiflorum* from QPS listing.

Young leaves and leaf buds of *Camellia sinensis* are used unfermented and dried to produce traditional “green tea” as the basis for traditional aqueous green tea infusions and for the manufacturing of dried green tea extracts for food supplement use. Although there are no significant health concerns associated with traditional consumption of green tea infusions, in recent years an association was seen between the intake of larger amounts of dried green tea extracts via food supplements to support weight-loss and the occurrence of liver damage. One component of green tea extracts, (-)-epigallocatechin-3-gallate (EGCG), the major catechin present, is associated with liver toxicity seen in animals and humans. EGCG is a thresholded substance with sufficient toxicity data to establish a health-based guidance value. Consequently dried green tea extracts from *Camellia sinensis*, following the scheme outlined in Figure 1 could be included in a QPS list with a qualification to protect against exposure to EGCG greater than the guidance value.

The exercise above shows that it would be possible to create a list of plants for which a presumption of safety could be established. For some botanicals, it may be possible to list individual species or groups of species from the same genus as is done for microorganisms, with the implication that use of the raw material or any extract of that material is presumed safe (subject to any qualification). However, in contrast to the QPS list for microorganisms, the number of compounds of concern and their potential for differential extraction would mean that only specific extracts could be included.

4. VALUE FOR EFSA

It has to be acknowledged that the pre-assessment of a very large number of botanicals and their preparations would be demanding of resources and time. Where use is likely to be restricted to sensory purposes the QPS approach, while possible, offers only limited advantages over the existing methodologies. Relatively few botanical preparations have multiple uses, particularly if feed applications are not considered. Consequently there are only a limited number of occasions when the same material is subject to assessment under different regulations and by different panels. Such few cases could be handled by normal processes within EFSA.

One of the major benefits of the QPS approach applied to microorganisms is that the presumption of safety could be applied to strains falling within a defined taxonomic unit regardless of intended use. A parallel situation for botanicals would be more rarely encountered and the scope of application for those materials listed is likely to be more restrictive. Inevitably this reduces the value of the QPS approach to safety assessment, as some applications may be covered by the pre-assessment and others not.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The principles used to establish the suitability of a microbial group for inclusion in a QPS list of microorganisms can be applied in a similar manner to botanicals and botanical preparations. However, the particularity of botanicals, which may be presented in a wide variety of forms and whose morphology and chemical composition may be markedly affected by geographical and environmental factors, makes the possibility of establishing QPS status at high taxonomic levels quite limited.

Using the above-mentioned principles, it has been possible to develop a structured assessment scheme (see Figure 1) applicable to botanicals and botanical preparations used in food which took as its starting point the existing EFSA Guidance document on the safety assessment of botanical supplements.

Reiterative applications of the structured safety assessment scheme to related botanicals or different botanical preparations obtained from the same plant variety can allow a Qualified Presumption of Safety status to be derived for specific botanical groupings.

When granting QPS status on the basis of history of use in the absence of reported adverse effect, it should be kept in mind that absence of evidence for adverse effect can not be taken as an evidence for the absence of adverse effect(s). The suitability for QPS status of e.g. preparations containing substances that show a pharmacological effect at doses close to the levels of exposure resulting from the traditional use should be carefully considered, as there is a biological plausibility for an adverse health effect, although it has not been picked up by historical data.

The exercise with examples carried out in the present opinion showed that it is possible to identify some plant species suitable for inclusion in a QPS list as is done for microorganisms. However, for other plants, because of the number of compounds of concern and their potential for differential extraction, only specific extracts were considered suitable for inclusion.

As with microorganisms, exclusion from a QPS list would not imply a botanical or botanical preparation is unsafe, but that a case-by case assessment of safety is required.

The use of botanicals and botanical preparations in animal feed is excluded from consideration at this stage. The lack of category-specific data and the potential differences in pharmacokinetics found amongst livestock including fish makes it unlikely that a composite conclusion necessary for a QPS approach could be achieved.

Relatively few botanical preparations have multiple uses, particularly when feed applications are not considered. Consequently there are only a limited number of occasions when the same material is subject to assessment under different regulations and by different panels. Such occasional duplications would not justify establishing a QPS list, as ensuring a uniformity of approach (and outcome) could be handled by existing processes within EFSA.

The pre-assessment of even a selected number of botanicals and their preparations would be very demanding of resources and time. Where use is likely to be restricted to sensory purposes the QPS approach, while possible, offers only limited advantages over the existing procedure and may not be cost-effective in the short term.

RECOMMENDATIONS

The structured safety assessment scheme provides a practical method of implementing the Level A of the 2009 EFSA Guidance on the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. Since the scheme is not constrained by historical levels of exposure, it also has potential application for the safety assessment of botanicals and botanical preparations in general. The Scientific Committee recommends that all panels dealing with botanicals are made aware of and encouraged to use the scheme.

The Scientific Committee also recommends that a reference list of botanicals that have been subject to a safety assessment within EFSA should be maintained. This could be of immediate value to those assessing the same or similar material for a different end use. It could also allow, in the longer term and as the number of botanicals assessed increases, a QPS list to be produced by default without the need for extensive pre-assessments.

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APPENDICES

Appendix A. Regulatory frameworks applicable to botanicals

If a QPS approach is to be adopted then it must be able to co-exist with requirements established by existing regulatory frameworks:

- **Directive 2002/46/EC** sets out labelling requirements and requires that EU-wide maximum and minimum levels are set for each vitamin and mineral added to supplements. The aim is to harmonise the legislation and to ensure that these products are safe and appropriately labelled so that consumers can make informed choices. Annex I lists the vitamins and minerals which may be used in the manufacture of food supplements. Annex II of Directive 2002/46/EC is a list of permitted vitamin or mineral substances that may be added for specific nutritional purposes in food supplements. It also allows the use for the same purpose of “other substances” with a nutritional or physiological effect, but definitions of such effects are not elaborated in the Directive. These two annexes have been replaced by the ones from **Regulation (EC) N° 1170/2009** that takes account of new vitamin and mineral forms evaluated by EFSA and comments received from interested parties.
- **Regulation (EC) N° 1925/2006** on the voluntary addition of vitamins and minerals and certain other substances to food (fortified food). Article 8 of Regulation, focused on so called “other substances”, foresees a specific procedure in order to prohibit, restrict or place under scrutiny a substance other than vitamins or minerals that is added to foods under conditions that would result in the ingestion of amounts of this substance greatly exceeding those reasonably expected to be ingested under normal conditions of consumption of a balanced and varied diet and/or would otherwise represent a potential risk to consumers. Member States can submit a request to the European Commission, providing scientific evidence allowing the Commission to classify a particular product in Annex III of the Regulation, in either:
 - Part A, when a harmful effect has been identified, and the addition of the products to food shall be prohibited,
 - Part B, when a harmful effect has been identified, and the addition of the products to food shall be allowed only under specific conditions,
 - Part C, if the possibility of harmful effects on health is identified but scientific uncertainty persists, and the substance shall be under Community scrutiny.

Many supplements are marketed for supposed health benefits and there may be overlap with herbal medicinal products which are regulated in a manner distinct from that used for most food/feed products or ingredients.

- **Directive 2004/24/EC** on “traditional herbal medicinal products” provides for definitions of (i) traditional herbal medicinal products, (ii) herbal medicinal products, (iii) herbal preparations and (iv) herbal substances. The directive introduces three categories of products: 1) a product can be classified under traditional medicinal use provisions (‘traditional use’) accepted on the basis of sufficient safety data and plausible efficacy (at least 30 years of use including at least 15 years within the Community), 2) a product can be classified under well-established medicinal use provisions (‘well-established use’). This is demonstrated with sufficient safety and

efficacy data, and 3) a product can be authorised after evaluation of a marketing authorisation application consisting of only product-specific safety and efficacy data ('full dossier').

- **Regulation (EC) N° 1924/2006** on nutrition and health claims made on food sets out the responsibility for EFSA to evaluate whether nutrition and health claims for foods are supported by sound science and, by doing so, to define the scientific requirements for the substantiation of claims. This regulation does not foresee an assessment of the safety of the product carrying the claim. Most of the claims submitted to the NDA Panel did not fulfil the criteria for scientific substantiation; their evaluation has been put on hold until the European Commission proposes an alternative solution.
- **Regulation (EC) N° 258/97** on novel foods is under a review process. It foresees a notification procedure to be introduced for foods which have not been traditionally sold in the EU but which have a safe history of safe use in third countries. "For traditional food from third countries, a safety assessment and management based on history of safe food use in the country of origin shall be introduced. If the history of safe food use in the country of origin has been demonstrated, and the Member States and EFSA do not present reasoned safety objections, based on scientific evidence, the food could be placed on the market by means of a notification of the food business operator intending to market the food"
- **Regulation (EC) N° 1831/2003** provides a Community procedure for authorising the handling and marketing and use of feed additives and to lay down rules for the post-authorisation monitoring and labelling of feed additives and their premixtures. EFSA has a key role in providing independent scientific advice to support the authorisation process for feed additives, evaluating both safety and efficacy.
- **Regulation (EC) N° 2232/96** sets out the main rules on the use of flavourings in foods in the EU. Based on this legislation a procedure was launched to establish an EU positive list of flavourings which will govern the flavourings that may be added to foods. This Regulation was amended by **Regulation (EC) N° 1331/2008** that introduced a common approval procedure for additives, enzymes and flavourings used in food, based on scientific opinions from EFSA, and **Regulation N° 1334/2008** establishing an EU list of authorised flavouring substances. Data required for the risk assessment of flavourings other than chemically defined flavouring substances (e.g. botanicals / botanical preparations from non-food sources) are outlined in the EFSA guidance document (EFSA CEF Panel, 2010).

Appendix B. Case studies for testing the proposed approach for QPS assessment

The following case studies are presented for the purpose to illustrate the applicability of the QPS approach to botanicals and botanical preparations. Data were collected for the purpose of this testing exercise only and are not the result of a structured data search. As such, the outcome of these QPS assessments should not be used elsewhere to support the safety of the botanicals and botanical preparations.

B.1 *Rosa canina*

Species, plant parts and preparations used

Rosa canina L.; fruit, excluding the seed.

Composition

- pectin
- sugars (sorbitol)
- fatty acids
- polyphenols (tannins) : proanthocyanidols and flavonoids
- vitamin C (ascorbic acid): 0,5 to 1,7 %, beta-carotene, vitamin B1, vitamin B2, vitamin B3 and vitamin K
- alpha-tocopherol,
- other organic acids: citric, malic.
- Minerals (Ca, Fe, K, Mn, Na, P, and Zn)

Toxicity

No toxicity reported. No reported adverse effect, apart from digestive tract and mouth irritation resulting from the ingestion of the hair-like layer under the flesh of the hips

Use

The fruit can be eaten as such (after having removed the hairs); or in various types of preparation such as dried, in infusion, soups, macerated in beer, wine, or in jam.

Result of evaluation

Adequate compositional, toxicological and use data available. No reported adverse effect.
Proposal to grant QPS without qualification for the fruit (excluding the seed) of *Rosa canina*.

Iteration process:

Chemical composition of the fruits of *Rosa* spp. appears to be rather stable (Ercisli, 2007).

Fruits of the following species can be safely consumed when used appropriately: *Rosa alba*, *Rosa centifolia*, *Rosa damascena* (American Herbal Products Association, 1997).

Flower petal use of *Rosa rugosa* is also categorised in class 1 of the Botanical Safety Handbook

Rose (hips and petals) have no known specific safety issues

Conclusion: Adequate compositional, adequate toxicity data (mostly based on history of safe use – absence of reported adverse effects) adequate use data available;

It is therefore proposed to extend QPS status without qualification to the following species for fruit and petal: *Rosa alba* L., *Rosa centifolia* L., *Rosa canina* L., *Rosa damascena* L., *Rosa dumalis* Bechst., *Rosa pisiformis* Sosn., *Rosa pulverulenta* M. Bieb., and *Rosa villosa* L.

B.2 *Rosmarinus officinalis*

Species, plant parts and preparations used

Rosmarinus officinalis L. Most scientific authorities recognise only the single species. Rosemary is available as various aqueous and non-aqueous preparations derived from the flowering dried twig tips, dried leaves, fresh leaves, the fresh aerial parts collected during flowering and the flowering branches. The essential oil of rosemary is distilled from the flowering tops or from stems and leaves of the plant taken before flowering.

Composition

Whole plant. Sufficient is known about the chemical composition of the aerial parts to recognise that the plant and its extracts contain substances of concern. The whole plant contains a range of flavonoids including diosmetin, diosmin, genkwanin and derivatives, luteolin and derivatives, hispidulin, neptin, nepitrin and apigenin). Other characteristic constituents are simple phenolic acids, phenolic diterpenes (carnosol, carnosolic acid, rosmanol, isorosmanol, epirosmanol, rosmaridiphenol, rosmariquinone), triterpenoids such as oleanolic and ursolic acids, α - and β -amyrin, and rofficerone and various hydroxycinnamic acid derivatives, e.g. rosmarinic acid.

Extracts. Characteristic components of the essential oil are: 1,8-cineole, α -pinene, camphor, bornyl acetate, borneol, camphene and α -terpineol. Limonene, β -pinene, β -caryophyllene and myrcene are also present. Some sources indicate *p*-cymene and linalool as important constituents. Solvent extraction generates products which differ significantly in comparison with the oil obtained through steam distillation. Notably the di- and tri-terpenes and triterpenic acids are selectively extracted while the volatiles typical of the essential oil are present only in low amounts.

Toxicity

Non-aqueous solvent extracts. The potential toxicity of non-aqueous extracts has been assessed by EFSA (2008). Five representative extracts were studied (acetone, ethanol alone or in combination with hexane and supercritical carbon dioxide). Extracts were non-genotoxic in a number of bacterial and mammalian test systems. Data from acute mouse toxicity studies (2), 14-day range finding studies in rats (2) and chronic oral toxicity studies in rats (6,) were examined. NOAEL values in the range 180 – 400 mg extract/kg BW per day were identified from the 90-day studies equivalent to 20 – 60 mg/ kg BW per day carnosic acid plus carnosol. A comparison of the estimated potential exposure of adults and children to Rosemary extracts compared to the NOAEL values indicate margins of 200 – 600 (95th percentile for adults) and 100 – 300 (95th percentile, pre-school children). The ANS Panel concluded that the use of non-aqueous solvent extracts of Rosemary could be safe in food and proposed maximum use levels. These have now been established in legislation (Commission Directives 2010/67/EU and 2010/69/EU).

Aqueous extracts. Aqueous extraction favours the solubilisation of rosmarinic acid which can reach 10% w/w of extracts. No oral toxicity studies made with aqueous extracts of Rosemary appear to have been reported other than a (very) preliminary examination of effects on the male rat when administered over five days at a dose level of 291.2 mg and 582.4 mg/kg of body weight. Rosemary extract at the lower dose did not affect body or organ weights, sperm production or food intake. At the

higher dose there was a significant increase in seminal vesicle weight. These data are insufficient to derive a safe level of intake.

Rosmarinic acid itself exhibits low toxicity (LD₅₀ in mice is 561 mg/kg for intravenous administration) and is not mutagenic. It is well absorbed from the gastrointestinal tract and through the skin. However there are no health-based guidance values for rosmarinic acid and insufficient toxicity data from which a safe dose could be derived.

Essential oil. Rosemary essential oil is contra-indicated for oral use. It is toxic even in fairly low doses, and a maximum safe dose has not been identified. Ingestion can result in stomach and intestinal irritation and kidney damage. Toxicity can be ascribed in part to camphor (and its metabolite borneol) and to the monoterpene ketones (limonene, α and β -pinene), which are convulsants, and have caused seizures in large doses. Rosemary is also an abortifacient based on its traditional use for abortion, as well as preliminary evidence showing embryotoxic effects. The oil provokes genotoxic and mutagenic effects when administered orally based on the results of a comet micronucleus assay and a bone marrow chromosome aberration test. Consequently use of the essential oil should be restricted to topical application and is not suitable for food use.

Use

Rosemary finds common use in food as a culinary herb, in beverages, and its extracts as food flavours, preservatives and antioxidants.

Result of evaluation

Aqueous extract: Composition well documented but, at present, there are insufficient data from which to derive a maximum safe intake. Based on the major component (rosmarinic acid), QPS qualification would have to be set based on the TTC approach.

Non-aqueous extract: QPS with a qualification would ensure compliance with set in Commission Directives.

Essential oil: Oral use contra-indicated and so should be excluded from the QPS approach.

Iteration process:

No iteration is required for the non-aqueous extracts as adequate toxicology based on a representative range of extracts is available on which to base an assessment.

Sufficient compositional data for the aqueous extracts are available and can be used to identify components of potential concern making an iterative approach possible. However, other than rosmarinic acid, little data are available for the identification of safe intake levels and consequently the assessment of individual components is likely to default to the TTC approach. Existing evidence would suggest that consumption of the essential oil is not desirable.

B.3 *Citrus aurantium*

Species, plant parts and preparations used

Citrus x aurantium ssp. *amara* (Link) Engl. (synonym: *Citrus aurantium* L.)

Dried hydro-alcoholic extracts of dried immature fruits and dried peel of the immature and mature fruit of *Citrus x aurantium* ssp. *amara* are available for food supplement use (Appendix A of the reference EFSA ESCO, 2009).

Composition

Bitter orange peel

An important constituent of the bitter orange peel is the essential oil. The pharmaceutically used bitter orange peel (*Aurantii amari epicarpium et mesocarpium*) being the dried epicarp and mesocarp of the ripe fruit of *Citrus x aurantium* ssp. *amara* partly freed from the white spongy tissue of the mesocarp and endocarp (Ph. Eur. 7, 2011) is said to contain 1.0-2.5 % essential oil (*Aurantii amari aetheroleum*, *Oleum Aurantii corticis*, *Oleum Aurantii amari*). The main component of the essential oil is limonene (up to 90 %). Several other monoterpenes are present (citral, linalool, linalyl-, neryl-, geranyl-, citronellyl-acetate). Aliphatic aldehydes and methyl-anthranilate determine the fragrance of the oil. Coumarins and furocoumarins are also found in the non volatile part of the essential oil. Meranzin, isomeranzin, epoxybergamottin and bergapten are the major coumarin- and furocoumarin derivatives found in the essential oil of bitter orange peel (Ph. Eur. Comment., 2012). Reported concentrations in bitter orange oil are 0.31 - 1.2% for meranzin, 0.15 – 0.22% for isomeranzin, 0.18 – 0.33% for epoxybergamottin and 0.05 - 0.1% for bergapten (Hager, 2006).

The bitter substances of the bitter orange peel are flavonoids (flavanones glycosylated with neohesperidose, e.g. naringin, neohesperidin, neoeriocitrin) and tetranortriterpenes (limonoids) (Hager, 2006).

(-)-Synephrine ((-)-p-methylaminoethanolphenol) and octopamine are the most frequently mentioned biogenic amines found in bitter orange peel, however, there is no evidence that octopamine or other phenethylamine alkaloids are present in bitter orange peel in any appreciable levels. Analyses of the dried peels of fruits and of dried fruits have shown a variation of the levels of (-)-synephrine from 0.1 to 2.0 %. (-)-synephrine and related alkaloids appear to be present in slightly higher quantities in the unripe fruit than in the ripe fruit. (-)-Synephrine is a sympathomimetic agent supposed to be responsible for the adrenergic effects of bitter orange food supplements. (NTP/NIEHS, 2004; Appendix A of the reference EFSA ESCO, 2009).

Extracts of bitter orange fruits and their peel for food supplement use

The extracts are usually standardised for their (-)-synephrine content. Some are additionally standardised for related adrenergic phenylethylamines (e.g. octopamine, hordenine). Commercial extracts are marketed with a content of 6-10 %, but can contain up to 95 % (-)-synephrine (NTP/NIEHS 2004, Blumenthal 2005). Other biologically active constituents present in the hydro-alcoholic extract of the (unripe) fruit of *Citrus aurantium* include flavonoid glycosides and low levels of furanocoumarins (Appendix A of the reference EFSA ESCO, 2009).

Toxicity

Animal and in vitro data

Animal experiments, such as a 28-days-NTP (National Toxicology Program)-study in rats (Hansen, 2012), show that *Citrus aurantium* extracts exhibit cardiovascular effects, but they do not allow identification of NOAEL values since the dosages chosen were too high.

No data are available on the genotoxicity of *Citrus aurantium* peel and its extracts.

For (±)-synephrine (racemate) (120 µM to 21.53 mM) no mutations were observed in L5178Y mouse lymphoma cells (McGregor et al., 1988).

Human data

From the human studies available, only clinical studies with a one-off intake of (-)-synephrine from *Citrus aurantium* extracts are reliable. There is a lack of suitable studies based on repeated and long-term intake of *Citrus aurantium* extract with (-)-synephrine. Following a one-off dose of 54 mg of (-)-synephrine in *Citrus aurantium* extract, healthy test persons without any physical exercise showed, compared to control, an average increase in systolic blood pressure of 7.3 mm Hg as well as slight acceleration of the pulse rate (Bui et al., 2006). Following administration of *Citrus aurantium* with 46.9 mg of (-)-synephrine, the pulse rate increased though not the blood pressure measured (Haller et al., 2005). At 27 mg of (-)-synephrine in *Citrus aurantium* extract given as a one-off dose, there were no differences with regard to the length of the QT interval in the electrocardiogram (ECG), or in relation to systolic and diastolic blood pressure (Min et al., 2004).

Use

In traditional food the whole mature and immature fruits and their peel are used e.g. in bitter-orange marmalades, liqueurs and in the form of candied orange peel. Total daily intake of (-)-synephrine via traditional food, considering maximum concentrations of (-)-synephrine, amounts to 6.66 mg/d for average consumers and to 25.7 mg/d for high consumers (BfR, 2012). These values take also intake of (-)-synephrine via sweet oranges, lemons, mandarins and clementines and their juices into account.

Extracts (water/alcohol) of dried immature fruits and/or peel of bitter orange have been used for food supplements, e.g. for herbal weight loss formulas (as an alternative to Ephedra). (-)-Synephrine is believed to be the active ingredient and to act as an agonist of adrenoceptors. Products are claimed to produce and/or maintain weight loss, improve physical fitness, and increase lean muscle mass. Such weight loss formulas usually contain 100-200 mg of bitter orange extract (NTP/NIEHS, 2004; Blumenthal, 2005). Often these products contain in addition caffeine which is expected to enhance the cardiovascular effects of (-)-synephrine (Health Canada, 2011; Appendix A of the reference EFSA ESCO, 2009).

In a medicinal product, the racemic mixture of (\pm)-synephrine having only about half of the biological activity of (-)-synephrine has been used in the form of the tartrate to treat cardiovascular disturbances (Rote Liste, 1995; Martindale, 2011; Stohs and Preuss, 2012). The recommended single dose is equivalent to 34.5 - 52 mg (-)-synephrine given three times daily, equivalent to a total dose of 103.5 - 155 mg (-)-synephrine/d.

Result of evaluation

Following the application of the flow diagram (Figure 1), (-)-synephrine extracted from *C. aurantium* can be classified as follows:

- thresholded substance
- no established health-based guidance value
- no sufficient toxicity data available to estimate a safe level of intake, but there is a history of use via traditional food without any reported adverse effect. It should however be underlined that absence of evidence for adverse effect can not be taken as an evidence for the absence of adverse effect(s). Considering the doses showing a pharmacological effect in humans and the levels of exposure resulting from the traditional use of *C.aurantium* preparations, there is a biological plausibility for an adverse health effect, although it has not been picked up by historical data.

A diversity of coumarin- and furocoumarin derivatives is described as components of the essential oil of *C. aurantium*. Theoretically these compounds could occur as minor impurities in the botanical preparation(s) considered, although no information could be retrieved to confirm their presence in *C.*

aurantium water/alcohol extracts. Still, coumarin and furocoumarin derivatives should be considered as substances of interest for the QPS assessment and run through the flow diagram (Figure 1).

Conclusions of the assessment:

- (-)-Synephrine is regarded as the principal substance of concern (grouped together with related adrenergic phenylethylamines, e.g. octopamine, hordenine). A diversity of coumarin- and furocoumarin derivatives is regarded as minor impurities which theoretically may occur. Their intake levels should stay below possibly existing health based guidance values, or below the relevant TTC values in the absence of such health-based guidance values.
- If basing the assessment on the history of use without any reported adverse effect, and in line with the level A of the SC guidance for the safety assessment of botanicals and botanical preparations (EFSA, 2009), dried hydro-alcoholic extracts of dried immature fruits and dried peel of the immature and mature fruits of *Citrus x aurantium* ssp. *amara* (Link) Engl. are suitable for QPS status, provided that the use of extracts is restricted to levels where (-)-synephrine intakes in the form of food supplement(s) do not exceed significantly historical intake levels from traditional foods.
- If one decide to ignore the history of use, considering rather the plausibility for undetected long term adverse effects linked to (-)-synephrine, dried hydro-alcoholic extracts of dried immature fruits and dried peel of the immature and mature fruits of *Citrus x aurantium* ssp. *amara* (Link) Engl. would then be excluded from QPS status.

Iteration process:

Extension of the QPS status for the dried hydro-alcoholic extracts to other preparations or the entire immature or mature dry or fresh fruits of *Citrus x aurantium* ssp. *amara* (Link) Engl. including their peels

The extension seems to be possible whereby this still needs verification examining the existing database.

Extension of the QPS status of entire immature or mature dry or fresh fruits *Citrus x aurantium* ssp. *amara* (Link) Engl. including their peels to other parts of *Citrus x aurantium* ssp. *amara* (Link) Engl.

The question of whether extension of the QPS status to other parts of the plant used, such as leaves (*Citri aurantii folium*) or flowers (*Aurantii amari flos*), is possible has to be evaluated based on relevant literature, e.g. comparing the composition data of the dried fruits and their peels with those of relevant other plant parts.

Extension of the QPS status of entire immature or mature dry or fresh fruits of *Citrus x aurantium* ssp. *amara* (Link) Engl. including their peels to fruits of other subspecies of *Citrus aurantium* L. or of other species of the genus of *Citrus*

Other subspecies of *Citrus aurantium* L., e.g. *Citrus x aurantium* ssp. *bergamia* (Risso & Poit.) Engl. (bergamot orange) or *Citrus aurantium* var. *voangkely* H. Perrier, are described. The genus *Citrus* comprises different species including many hybrids of which some are the source of edible, others of non edible fruits. According to Tanaka (1954) the term *Citrus* is a genus comprising 145 species (and 12 additional new species) of which the fruits are edible or not edible. According to Swingle (1967) the term *Citrus* is more specifically defined as a subgenus comprising only 16 species which are all the source of edible fruits with the exception of the species of *Citrus tachibana* (Hager, 2006).

Besides the fruits of *Citrus aurantium* L. also the fruits of other *Citrus* species may contain (-)-synephrine. Arbo et al. (2008) identified (-)-synephrine in the fruits of all *Citrus* species they investigated: *Citrus aurantium* L., *C. sinensis* Osbeck, *C. deliciosa* Ten, *C. limon* Burm and *C. limonia* Osbeck. (-)-Synephrine was also found by Xing-Qian et al. (2011) in the fruits of all nine mandarin cultivars they analysed: *C. unshiu* var. *praecox* Tanaka cv Nichinan No. 1, *C. unshiu* var. *praecox*

Tanka cv Miyagawa wase, *C. unshiu* Marc. cv Yamada, *C. unshiu* Marc. cv Owari, *C. poonensis* Hort. ex Tanaka, *C. erythrosa* Hort. ex Tanka, *C. tardiferax* Hort. ex Tanka, *C. succosa* Hort. ex Tanaka, *C. suavissima* Hort. ex Tanaka.

(-)-Synephrine has also been detected by Inafuku-Teramoto et al. (2011) in the peel of the fruits of all the analysed *Citrus* species: *C. depressa*, *C. madurensis*, *C. rokugatsu*, *C. oto*, *C. keraji*, *C. nobilis*, *C. tankan*, *C. tangerine*.

Other typical components of fruits belonging to the genus of *Citrus* in a wider sense are (i) essential oils and their characteristic ingredients such as terpenes, (ii) typical flavonoids such as a diversity of flavanones, flavones and flavonoles, (iii) coumarin derivatives such as different furocoumarins and hydroxycoumarins, and (iv) a diversity of limonoids (Hager, 2006).

In view of the expected diversity in composition of the fruits of the numerous *Citrus* species/subspecies including all hybrids, and the biological activities of the components which may be present, it can only be decided on a case by case basis for each species and subspecies if it will be justified to extrapolate the above described QPS approach to it and if an implication of additional or other qualifications is necessary. A literature research would be needed regarding e.g. the composition of the fruits of the different individual *Citrus* species/subspecies to conclude which of them could be included in the QPS approach. This would be most promising in a first step for the edible fruits of *Citrus* species/subspecies.

B.4 *Foeniculum vulgare*

Species, plant parts and preparations used

For *Foeniculum vulgare* two varieties can be defined including *Foeniculum vulgare* Mill. var. *dulce* and *Foeniculum vulgare* Mill. var. *vulgare*. From both species preparations based on the essential oil as well as preparations containing water based extracts might be considered.

Composition

Essential oil

The essential oil of both species is known to contain substances of concern including *trans*-anethole and estragole (SCF, 2001a; SCF, 2001b; Council of Europe, 2006). The essential oil also contains estragole which is known to be genotoxic and carcinogenic.

Water based extracts

Given the limited water solubility of these compounds of concern their concentrations in water extracts is expected to be significantly lower than in the essential oils.

Toxicity

For *trans*-anethole JECFA derived a temporary ADI of 0-2.0 mg/kg bw (JECFA, 1998), which can be used to define whether exposure of proposed uses and use levels will be safe and can be assigned QPS status with defined exposure restrictions.

For estragole there are carcinogenicity data from which a BMDL₁₀ could be derived and one could use the MOE approach to characterise the level of concern resulting from the exposure to this substance through food. However, given the recommendation of the Scientific Committee to not introduce into the food chain substances that are known to be genotoxic and carcinogenic (EFSA, 2005), preparations from *Foeniculum vulgare* containing estragole will have to be excluded from the QPS approach and therefore subject to a case-by-case assessment

Use

Fennel based teas are traditionally used in many parts of Europe including France, Germany, Austria, Czech Republic and Poland in for example the symptomatic treatment of digestive disorders alleviating mild spasmodic gastro-intestinal ailments and for the relief of symptoms during inflammations of mucous membranes of the upper respiratory tract (EMA, 2008). Homemade fennel tea is often used as a remedy for gastrointestinal complaints in infants and young children (Crotteau et al., 2006; Perry et al., 2011). In addition various fennel-based food supplements are on the market containing for example the essential oil, dried extract or seeds.

Result of evaluation

Given the recommendation of the Scientific Committee to not introduce into the food chain substances that are known to be genotoxic and carcinogenic (EFSA, 2005), preparations from *Foeniculum vulgare* containing estragole are excluded from the QPS approach and should be subject to a case-by-case assessment. In this particular case, it should be noted that the level of estragole extracted into the essential oils of *Foeniculum vulgare* species will be higher than the levels extracted into water based preparations. For risk management purposes, it may be of interest to assess preparations of these species on a case-by-case basis, using the carcinogenicity data for estragole from which a BMDL₁₀ could be derived and for which it is therefore possible to apply the MOE approach. The fact that some preparations e.g. essential oils of *Foeniculum vulgare* and *Ocimum tenuiflorum* species will show higher levels of estragole than the levels extracted into (traditional) water based preparations should then be taken into account.

Iteration process: Given that different preparations (e.g. fine cut, whole fruits) and two varieties exist for *Foeniculum vulgare* generally used for fennel based teas, QPS status could be considered only if specific preparations of one or the other variety are demonstrated to be exempt of estragole.

B.5 *Camellia sinensis*

Species, plant parts and preparations used

Camellia sinensis (L.) O. Kuntze

Parts used and preparations thereof: Young leaves and leaf buds are used unfermented and dried to produce traditional “green tea” as the basis for traditional aqueous green tea infusions. Leaves and leaf buds are also used to produce the so called “dried aqueous green tea extracts” for use in food supplements. (Appendix B of the reference EFSA ESCO, 2009).

Composition

Green tea

Polyphenols: Green tea contains a diversity of polyphenolic compounds, which account for up to 30% of the dry weight of green tea leaves. Most of the polyphenols in green tea are flavanols, commonly known as catechins. The primary catechins in green tea are (-)epicatechin (EC), (-)epicatechin-3-gallate (ECG), (-)epigallocatechin (EGC), and (-)epigallocatechin-3-gallate (EGCG). Furthermore (+)catechin (C), (+)gallocatechin (GC), (-)gallocatechingallate (GCG), (-)catechingallate (CG), occur in green tea. Young leaf green tea contains lower levels of EGCG and total catechins than old leaf green tea (Lin et al., 2003).

Purine alkaloids: caffeine (previously referred to as theine or teine; depending upon the development stage of the leaves, 2.9-4.2%, content declining with age), theobromine (0.15-0.2%), theophylline (0.02-0.04%).

Amino acids: The total amino acids content in green tea amounts to 4%, including the tea characteristic L-theanine as a major component (2% of green tea).

Green tea extracts

Green tea extracts, e.g. traditional aqueous green tea infusions or dried green tea extracts, vary in their compositions depending on the green tea used and the conditions of the manufacturing procedure.

Table 1: Contents (mean values of 3-5 determinations) of catechins in a Chinese and a Japanese green tea infusion (preparation: 1g tea leaves were brewed with 100 ml boiling water and decanted after 5 minutes). The (+)-catechin contents are below the detection limit (10 µg/ml). ^a = percentage referred to total catechins. (Khokar et al., 1997).

Green tea infusions	EC (mg/100 ml)	ECG (mg/100 ml)	EGC (mg/100 ml)	EGCG (mg/100 ml)	Total catechins (mg/100 ml)
China	4.7 (9.1 %) ^a	4.4 (8.5 %) ^a	16.3 (31.7 %) ^a	26.3 (51.1 %) ^a	51.5
Japan	9.4 (11.1 %) ^a	5.9 (6.9 %) ^a	28.7 (33.8 %) ^a	40.8 (48.1 %) ^a	84.9

The manufacturing processes for “dried green tea extracts” for use in food supplements vary in extraction techniques and manufacturing procedures and are not uniform. They may differ from the traditional green tea infusion, e.g. in the solvent being different from water, in the source (e.g. fresh leaves instead of green tea), in extraction conditions (e.g. degree of comminution, concentration ratios, temperature, duration, stirring) and in fractionation procedures concentrating active compounds (Appendix B of the reference EFSA ESCO, 2009).

Toxicity

Dried green tea extracts

Toxicokinetic results in animals and humans show that administration of concentrated green tea extracts under fasting conditions leads to a significant increase of plasma concentrations and bioavailability of EGCG compared to administration with feed or food (Appendix B of the reference EFSA ESCO, 2009).

Animal and in vitro data

In three subchronic studies in rats and fasting beagle dogs, NOAELs ranging from 40 to 50 mg EGCG/kg body weight per day have been found in relation to organ damage including hepatic necrosis (McCormick et al., 1999; Johnson et al., 1999; Isbrucker et al., 2006; Appendix B of the reference EFSA ESCO, 2009).

A green tea preparation (consisting of 85 to 95% total catechins (by weight) and more than 55% EGCG) was negative in the Ames test, the rat micronucleus assay, the UDS test, and the transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay (FDA, 2006; Chang et al., 2003). In an oral (gavage) carcinogenicity study, the same preparation was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day. The treatment was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined (FDA, 2006).

Human data

The analysis of the available human data (up to 2009) shows that in more than 30 cases, an association was seen between the intake of large amounts of green tea-derived products and the occurrence of, in some cases, severe liver damage. In many cases of these liver disorders dried green tea extracts with high EGCG contents were taken in capsule form over several months as a medicinal product or food supplement to support weight-loss. Concerning the treatment with an oral phytotherapeutical drug the daily intake of 2 capsules to 5 capsules (187.5 – 468.75 mg EGCG/ day), mostly 4 capsules (375 mg EGCG/ day) was associated with liver damage. A causal relationship has to be regarded as probable in 7 cases and as possible in 27 cases (Sarma et al., 2008; Appendix B of EFSA ESCO, 2009).

Use

Worldwide long-time consumption of traditional green tea infusions has to be taken into consideration. Beverages prepared from dried aqueous green tea extracts (ready to drink or prepared from instant preparations) show a similar composition, i.e. do not exceed the concentrations of polyphenols in traditional infusions, and are therefore under qualitative and quantitative aspects equivalent to traditional green tea infusions.

Exposure data exist for traditional uses as a stimulant drink in the form of green tea infusions (see Table 4 of Appendix B of the reference EFSA ESCO, 2009).

Food supplements or related products on the basis of dried green tea extracts, e.g. for the purpose of supporting weight reduction, have been described with a daily dose representing the equivalent of minimum 150 mg caffeine, 115-270 mg EGCG, and 375 mg catechins) (Appendix B of the reference EFSA ESCO, 2009).

A medicinal weight-loss product containing a high-dosed hydroalcoholic extract of green tea was marketed only until April 2003, when the French and Spanish authorities suspended the market authorisation because of hepatotoxic side-effects (AFSSAPS, 2003; Sarma et al., 2008).

Result of evaluation

(-)Epigallocatechin-3-gallate (EGCG) is the major catechin in green tea extracts and is associated with liver toxicity seen in animals and humans after exposure with dried green tea extracts under certain conditions.

Classification of EGCG found in dried green tea extracts for food supplement use according to the decision tree:

- thresholded substance
- established health-based guidance value

In the evaluation of dried green tea extracts for food supplement use, reference to a NOAEL ranging from 40 to 50 mg EGCG/kg body weight per day according to the results of three out of five subchronic studies is made (Appendix B of the reference EFSA ESCO, 2009). By applying a safety factor of 100, a maximum intake of 0.5 mg EGCG/kg body weight per day with dried aqueous green tea extracts used in food supplements can be accepted under the conditions that the extracts are manufactured under the same extraction conditions as applied in the traditional preparation of green tea infusions and that the extracts are not used for products for weight reduction purposes (Appendix B of the reference EFSA ESCO, 2009).

Conclusion of the assessment: apart from the worldwide long-time consumption of traditional green tea infusions⁴, which is regarded as safe⁵, QPS status could be granted to dried extracts of unfermented and dried leaves and leaf buds of *Camellia sinensis* (L.) O. Kuntze with the following qualifications:

- a maximum intake of 0.5 mg EGCG/kg body weight per day with dried aqueous green tea extracts used in food supplements.
- the extracts are manufactured under the same extraction conditions as applied in the traditional preparation of green tea infusions.
- The attention of the risk manager should be brought to the increased bioavailability of EGCG when taken in the fasting state.
- In addition the possible presence of caffeine in the dried extracts has to be taken into consideration.

Iteration process:

Extension of the QPS status of dried aqueous extracts of unfermented dried leaves and leaf buds of Camellia sinensis (L.) O. Kuntze to the entire unfermented dried or fresh leaves and leaf buds of *Camellia sinensis* (L.) O. Kuntze

Considering the available database this seems not to be possible.

Extension of the QPS status of dried aqueous extracts of unfermented dried leaves and leaf buds of Camellia sinensis (L.) O. Kuntze to extracts of a) fermented/semifermented dried leaves and leaf buds or b) of other parts of *Camellia sinensis* (L.) O. Kuntze

Depending on the manufacturing process mainly three different traditional tea products are prepared from the leaves and leaf buds of *C. sinensis*: Green tea, black tea and oolong tea. While “green tea” is produced without fermentation and thus preventing oxidation of the polyphenolic components, “black tea” manufacture is carried out by fermentation ensuring a high degree of enzymatically catalysed aerobic oxidation of the polyphenols followed by a series of chemical condensations. In “oolong tea”, a semifermented tea, polyphenols are partially oxidized. Thus unfermented, semifermented and fermented dried leaves and leaf buds of *C. sinensis* differ in their chemical composition as do their extracts.

The question of whether extension of the QPS status to extracts of fermented/semifermented dried leaves and leaf buds or of other parts of the plant, such as blossoms or roots, is possible, has to be evaluated based on relevant literature and comparing the composition data of the botanicals and their extracts.

Extension of the QPS status of dried aqueous extracts of unfermented and dried leaves and leaf buds of Camellia sinensis (L.) O. Kuntze to extracts of leaves and leaf buds of other species of the genus *Camellia*

The genus *Camellia* comprises about 80 different species (Hager, 2006) of which only the species *Camellia sasanqua* Thunb. containing sasanqua triterpenoid saponins, is listed besides *Camellia sinensis* (L.) O. Kuntze in the EFSA Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements (EFSA Scientific Committee, 2012). In view of the expected diversity in composition of the leaves and leaf buds of the numerous *Camellia* species and the biological activities of the components which

⁴ Beverages prepared from dried aqueous green tea extracts (ready to drink or prepared from instant preparations), that have a similar composition and do not exceed the concentrations of polyphenols in traditional infusions, are regarded to be equivalent to traditional green tea infusions

⁵ ² This conclusion holds provided that pregnant and nursing mothers as well as children and other caffeine sensitive persons consume the beverage in moderation or abstain from it (general recommendation for caffeine containing beverages postulated to be common knowledge).

may be present, it can only be decided on a case by case basis for each species if it will be justified to extrapolate the above described QPS approach to it and if an implication of additional or other qualifications is necessary. A literature research would be needed regarding e.g. the composition of the leaves and leaf buds of the different individual *Camellia* species to conclude which of them could be included in the QPS approach.

B.6 *Ocimum tenuiflorum*

Species, plant parts and preparations used

Ocimum tenuiflorum L. (Synonym *Ocimum sanctum* L.)

Parts used: Leaf: spice (Thai cuisine) but also used in traditional systems like the Indian Ayurveda (Pattanayak et al. 2010). Essential oil from leaf (EFSA, 2012).

Composition

Leaf: 2% Essential oil (EFSA 2012), 2% ursolic acid, a pentacyclic triterpenoid (3 β)-3-hydroxy-urs-12-en-28-oic acid) (Silva *et al.* 2008). The essential oil contains eugenol (up to 62%) and methyleugenol (up to 86%), 7-25% methylchavicol (estragole) and 7-23% 1,8-cineole (eucalyptole) (EFSA, 2012, Zheljazkov *et al.* 2008). The leaf is also reported to contain alkaloids and saponins (EFSA, 2012).

Toxicity

Reproductive toxicity

Leaves are used as a human abortifacient in India (Prakash & Gupta 2005, Ahmed *et al.* 2002b). There is no information on the doses used.

A preliminary study using fresh leaves 1 g/kg body weight/day resulted in vaginal bleeding. Feeding with fresh leaves of *O. tenuiflorum* (1 g/kg bw) twice a week for one month in adult rabbits caused significant changes in the histology of the testis, epididymis, uterus and ovary. Pregnancy and subsequent delivery occurred only in those rabbits which were allowed to mate one month after the stoppage of the leaves feeding period as compared to those rabbits allowed to mate directly after the stoppage of the feeding period (Reghunandan *et al.* 1997). This indicates that the effect under certain condition might be reversible (EFSA ESCO, 2009).

Other studies in male rats, mice and rabbits have shown various effects on male fertility, decreased sperm count, weight changes and/or histological effects on testes or accessory sex organs after peroral intake of the dried leaf and stem, with benzene extracts and water extracts (Khanna *et al.* 1986, Kantik and Gogate 1992, Ahmed *et al.* 2002a,b, Ahmed *et al.* 2009, Sethi *et al.* 2010, Pragma *et al.* 2012). The dried leaf and stem caused effect on oestrus cycle and fertility in female rats (Khanna *et al.* 1986).

Genotoxicity and carcinogenic effects

The genotoxicity and carcinogenicity of methyleugenol have been well documented (SCF 2001b, Rietjens *et al.* 2008).

Use:

No exposure data exist for use as a spice/culinary herb in Thai cuisine.

Therapeutic/medicinal use: Fresh leaves 2 g/kg body weight/day for 30 days (Sethi *et al.* 2008). Dried leaves: 300-2000 mg/day as a single dose and 600-2000 mg in multiple doses. Infusions 2 g dried leaf per cup of water or 2.5 g dried leaf/day. Leaf juice: 10-20 ml of fresh leaf juice (EFSA, 2012). No information on recommended dose levels of other plant parts.

Result of evaluation

The plant species and the plant parts are well-defined (first box in flow diagram).

The chemical analytical data do not provide adequate compositional data. The chemical(s) of concern for the reproductive effects have not been pinpointed. The information on compositional/toxicological/use data is insufficient. Moreover, *O. tenuiflorum*'s leaves are reported to contain genotoxic and carcinogenic substances. *O. tenuiflorum* L. (leaf) is therefore excluded from the QPS approach.

Iteration process:

Not applicable due to inadequate compositional/toxicological/use data.

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GLOSSARY

History of safe use	The safety of the food in question is confirmed with compositional data and from experience of use and continued use for at least 25 years in the customary diet of a large part of the population of a country	Council of the European Union (2009). Proposal for a Regulation of the European Parliament and of the Council on novel foods and amending Regulation (EC) No 1331/2008 (common position)
Margin of exposure	Ratio of the no-observed-adverse-effect level or benchmark dose lower confidence limit for the critical effect to the theoretical, predicted or estimated exposure dose or concentration.	FAO/WHO International Programme on Chemical Safety, 2009. Environmental Health Criteria 240 – Principles and Methods for the Risk Assessment of Chemicals in Food. ISBN: 978-92-4-157240-8
Margin of safety	The margin between the health-based guidance value (reference dose) and the actual or estimated exposure dose or concentration.	FAO/WHO International Programme on Chemical Safety, 2009. Environmental Health Criteria 240 – Principles and Methods for the Risk Assessment of Chemicals in Food. ISBN: 978-92-4-157240-8

ABBREVIATIONS

ANS	Panel on Food Additives and Nutrient Sources Added to Food	MOS	Margin of Safety
BMDL ₁₀	Lower confidence bound of the benchmark dose for a 10% response	NDA	Panel on Dietetic Products, Nutrition and Allergies
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids	QPS	Qualified Presumption of Safety
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed	(Q)SAR	(Quantitative) Structure Activity Relationship
MOA	Mode of Action	SC	Scientific Committee
MOE	Margin of Exposure	TTC	Threshold of Toxicological Concern