

## SCIENTIFIC OPINION

# Guidance on Safety assessment of botanicals\* and botanical preparations\*\* intended for use as ingredients in food supplements<sup>1</sup>

EFSA Scientific Committee<sup>2</sup>

European Food Safety Authority (EFSA), Parma, Italy

This guidance document published on 9 September 2009, replaces the earlier version published on 20 June 2008 with the Question Number: EFSA-Q-2005-233.

### ABSTRACT

In this opinion, EFSA's Scientific Committee provides guidance on the scientific data needed to carry out a safety assessments of a botanical or a botanical preparation. It also proposes a two-tiered scientific approach for the safety assessment depending on the available knowledge on a given botanical and the substance(s) it contains. The guidance also provides a set of criteria to help prioritise the safety assessment of botanical ingredients which are in use. EFSA has also compiled the available information on a large number of botanicals which have been reported to contain substances that may be of health concern when used in food or food supplements. The resulting compendium, which will be regularly updated, should be considered as part of this guidance document and is intended to assist manufacturers and food safety authorities by highlighting possible safety issues which may require further consideration.

### KEY WORDS

Botanicals, botanical preparations, safety assessment, food supplements, toxicological properties, medicinal properties.

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\* This terminology includes all botanical materials (e.g. whole, fragmented or cut plants, plant parts, algae, fungi and lichens);

\*\* This terminology includes all preparations obtained from botanicals by various processes (e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation).

1 On request of EFSA, Question No EFSA-Q-2009-00668, adopted on 22 July 2009.

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For citation purposes: EFSA Scientific Committee; Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. EFSA Journal 2009; 7(9):1249. [19 pp.]. doi:10.2093/j.efsa.2009.1249. Available online: [www.efsa.europa.eu](http://www.efsa.europa.eu)

## SUMMARY

Following the discussion paper of the Scientific Committee on botanicals and botanical preparations adopted on 23 June 2004, The European Food Safety Authority (EFSA) asked in August 2005 the Scientific Committee to develop a two-level tiered approach for the safety assessment of botanicals and botanical preparations. This approach consists of a first safety assessment level based on available knowledge and a subsequent level in which the safety assessment includes newly generated data.

The present guidance document is focussed on botanicals and botanical preparations intended for use in food supplements, although the approach chosen is, in principle, applicable also to other uses of botanicals and botanical preparations in the food and feed areas.

A general framework for safety assessment is proposed by the Scientific Committee, in which 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. Issues that should be carefully considered in order to reach such a conclusion are discussed in detail in the present guidance document. Botanicals and botanical preparations for which a presumption of safety is not possible based on available knowledge would be subject to a more extensive safety assessment, requiring additional data to be provided.

It is not the objective of this opinion to produce a list of safe botanicals and botanical preparations intended for food supplement use, but only to provide guidance on how to assess safety of botanical ingredients.

The Scientific Committee developed criteria for prioritising botanicals for safety assessment and has compiled a Compendium of botanicals that are reported to contain toxic, addictive, psychotropic or other substances that may be of concern. The main purpose of the Compendium, which should be considered as part of this guidance document, is to draw attention to issues that would need to be taken into account when assessing the safety of botanicals used as ingredients in food supplements, and to facilitate the establishment of priorities for safety assessment.

The Scientific Committee recommends maintaining the Compendium up-to-date, making use of relevant available national lists of plants and of any other relevant data available, as well as of updated assessments carried out on botanicals by qualified bodies. The Scientific Committee also recommends to further expand the Compendium with botanicals not having any market history in Europe but having a documented history of use in their third country of origin.

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## BACKGROUND AS PROVIDED BY EFSA

A discussion paper by the Scientific Committee on botanicals and botanical preparations widely used in food supplements and related products was adopted on 23 June 2004 (SC document EFSA/SC/26 Final<sup>3</sup>). In this paper, the Committee expressed concerns about quality and safety issues of botanicals and botanical preparations that have become widely available to consumers through several distribution channels in the EU. The use of botanicals and botanical preparations in food is regulated under the General Food Law (178/2002/EC), which attributes the primary legal responsibility for the safety of the products placed on the market to business operators. The Regulation however does not provide any guidance on how the safety of these products should be assessed. As the market volume and the variety of products expand, so does the need for a better characterisation of the range of botanicals and botanical preparations on the market, and for harmonising the risk assessment and consumer information approaches for these products. The paper aimed at increasing awareness of EFSA's Advisory Forum on potential public health aspects associated with these products.

The Secretariat brought the discussion paper to the attention of the Advisory Forum at its meeting of the 1<sup>st</sup> of October, 2004 (Document AF 01.10.2004 – 3a<sup>4</sup>). Simultaneously, an invitation (Document AF 01.10.2004 – 3<sup>5</sup>) was sent to the members of the Advisory Forum to take note of the concerns raised by the Scientific Committee and to complete a questionnaire (annexed to cover note AF 01.10.2004 – 3) to provide a better understanding of the issue in Europe.

By the end of January 2005, replies were received from twenty five countries, comprising twenty two EU Member States and three EFTA Countries. The members of the Advisory Forum underlined the importance of this issue for their countries and asked EFSA to initiate a self-task in order to develop some guidance on how to assess the safety of botanical ingredients.

Following the mandate received by the Scientific Committee in August 2005<sup>6</sup> from EFSA, the Scientific Committee developed a two-level tiered approach for the safety assessment of botanicals and botanical preparations. A guidance document focussing on botanicals and botanical preparations intended for use as food supplements was published after public consultation<sup>7</sup>.

A conceptual framework for safety assessment was advocated, in which 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 (first level of the framework). Issues that should be carefully considered in order to reach such a conclusion were discussed in detail in the guidance document. Botanicals and botanical preparations for which a presumption of safety is not possible would be subject to a more extensive safety assessment, based on additional data to be provided in accordance with the methodology described in the second level of the proposed framework.

As a follow up, it was decided to test the adequacy of the above-mentioned approach described in the guidance document for safety assessment with a selected number of examples including botanicals known to contain toxic substances or having a reported toxic effect, botanicals with an established history of food use, and botanicals that are known to contain potentially genotoxic/carcinogenic substances. To this end, an EFSA Scientific Cooperation (ESCO) Working Group, composed of experts identified by the members of the Advisory Forum and by the Scientific Committee EFSA was established in April 2008<sup>8</sup>. This working group was also given the task to finalise the Compendium of botanicals reported to contain toxic, addictive, psychotropic, or other substances of concern. The

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<sup>3</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1211902585418.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902585418.htm)

<sup>4</sup> See [http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/af10\\_doc3a\\_botanicals\\_en1.pdf?ssbinary=true](http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/af10_doc3a_botanicals_en1.pdf?ssbinary=true)

<sup>5</sup> See [http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/af10\\_doc3\\_botanicals\\_en1.pdf?ssbinary=true](http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/af10_doc3_botanicals_en1.pdf?ssbinary=true)

<sup>6</sup> See <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2005-233>

<sup>7</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1178669754855.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178669754855.htm)

<sup>8</sup> See [http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/esco\\_mandate\\_botanicals.pdf?ssbinary=true](http://www.efsa.europa.eu/cs/BlobServer/DocumentSet/esco_mandate_botanicals.pdf?ssbinary=true)

resulting ESCO report and Compendium<sup>9</sup> were provided to the EFSA Executive Director in May 2009.

#### **TERMS OF REFERENCE AS PROVIDED BY EFSA**

The Scientific Committee has been requested in May 2009<sup>10</sup> by the European Food Safety Authority to consider the recommendations made in the ESCO report for updating the guidance document for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements.

#### **ACKNOWLEDGEMENTS**

The European Food Safety Authority wishes to thank the members of the EFSA Scientific Cooperation (ESCO) Working Group on Botanicals and Botanical Preparations for the preparation of the ESCO Report<sup>9</sup>, which was used by the Scientific Committee to update this guidance document.

The European Food Safety Authority would also like to thank the members of the former Scientific Committee for their contributions to the present guidance document.

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<sup>9</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1211902876819.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902876819.htm)

<sup>10</sup> See <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2009-00668>

## ASSESSMENT

### 1. Introduction

The Scientific Committee decided to focus its work first on the safety assessment of botanicals and botanical preparations used as ingredients in food supplements<sup>11</sup> (hereafter referred to, as botanical ingredients), although the approach chosen is, in principle, applicable also to other uses of botanicals and botanical preparations in the food and feed areas. It is not in the scope of the present guidance to address issues related to quality assurance and good hygienic practices currently regulated by the EU Food Legislation, nor to assess the safety of food supplements as end products. The present guidance does not therefore address hazards linked to the presence of contaminants and foodborne pathogens in the botanicals and botanicals preparations.

A two-level tiered conceptual framework for safety assessment consisting of a safety assessment based on available knowledge and a subsequent level in which further testing and/or data are required is proposed by the Scientific Committee. Botanicals or botanical preparations for which an adequate body of knowledge exists, can benefit from a “presumption of safety” without any need for further testing. Based on reasonable evidence, they can then be assumed to be safe, sometimes under certain restrictions. The Scientific Committee used as an example the Qualified Presumption of Safety (QPS) approach developed for microorganisms in food and feed (EFSA, 2007a) to propose criteria for presuming a botanical or a botanical preparation safe. Botanicals and botanical preparations for which a presumption of safety is not possible should be subject to a more extensive safety assessment, based on additional data to be provided according to the methodology described by EFSA. By proposing a first safety assessment level based on available knowledge, the approach proposed by the Scientific Committee for the safety assessment of botanicals and botanical preparations is in line with EFSA’s policy to stimulate food and feed risk assessment approaches that minimise the number of experimental animals and any suffering (EFSA, 2009).

In order to facilitate the implementation of the above-mentioned approach, EFSA has also compiled a Compendium of botanicals and botanical preparations that have been reported to contain toxic, addictive, psychotropic or other substances that may be of concern. This Compendium should be seen as a tool to gather relevant information and define priorities for safety assessment. The inclusion of a botanical in this Compendium does not imply that it is not safe for use in food supplements. Without prejudice to the existing legal framework, such Compendium has no legal status and may not be used as support or evidence in any disagreement or dispute pertaining to the legal classification of products or substances.

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<sup>11</sup> Food supplement: Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities. (Directive 2002/46/EC)

## **2. Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements**

It should be noted that Regulation 258/97/EC concerning novel foods and novel food ingredients applies to all foods, including food supplements, containing substances which have not been used for human consumption to a significant degree within the Community before 15 May 1997 and which fall under certain categories specified in the above-mentioned Regulation. In the case of a proposed use as a novel food, botanicals or botanical preparations should be assessed following the guidelines of the Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients<sup>12</sup>.

Moreover, Regulation 1829/2003/EC on genetically modified food and feed would apply to any GMO ingredients used in food supplements. In the case of botanicals or botanical preparations derived from genetically modified plants, information should be provided in line with the guidance document of the EFSA Scientific Panel on Genetically Modified Organisms for the risk assessment of genetically modified plants and derived food (EFSA, 2006a).

When the botanical or botanical preparation is intended for use as a food intended for particular nutritional uses (PARNUTS – Directive 89/398/EEC), the guidance document from the Scientific Committee on Food on submissions for safety evaluation of sources of nutrients or of other ingredients proposed for use in the manufacture of foods (SCF, 2001a) should also be consulted.

It should also be underlined that this report only deals with guidance on safety assessment, whereas the scientific substantiation of any claims made on food supplements, as required by the Regulation on Nutrition and Health Claims<sup>13</sup>, will be dealt with in separate EFSA documents, such as the “Scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim” (EFSA, 2007b).

It is not the objective of this report to produce a list of safe botanicals and botanical preparations intended for food supplement use, but only to provide guidance on how to assess safety of botanical ingredients. Moreover, priority criteria are proposed, and a Compendium has been compiled to serve as a preliminary tool for risk assessors (see section 3).

### **2.1. Proposed data requirements for safety assessment of botanicals and botanical preparations used as ingredients in food supplements**

It is understood that the use of botanicals and botanical preparations as ingredients in food supplements will have to be in compliance with the existing EU Food Legislation<sup>14</sup>. This would include maximum permissible levels of chemical and biological contaminants (e.g. pesticides, mycotoxins, heavy metals and foodborne pathogens), modalities for ensuring quality, and application of good hygienic practice, including HACCP methodologies. The issues of controls needed to ensure constancy over time of the composition of botanical food supplements on the market and batch-to-batch variation are not addressed in this document as these are risk management aspects and therefore outside the scope of EFSA.

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<sup>12</sup> See <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997H0618:EN:HTML>

<sup>13</sup> See [http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/l\\_012/l\\_01220070118en00030018.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/l_012/l_01220070118en00030018.pdf)

<sup>14</sup> See e.g. Reg. 178/2002, Reg. 852/2004, Reg. 853/2004, Reg. 854/2004.

The following sections aim at identifying data and information considered as necessary to assess the safety of botanical ingredients. These data are of: (i) technical; (ii) exposure and (iii) toxicological nature. The lists below are meant to give guidance on data requirements. They have been made as exhaustive as possible and should be adapted on a case-by-case basis, depending on the nature of the botanical or botanical preparation. This implies that not all the information listed below would be needed in all cases and that the amount of information available for a given botanical or botanical preparation may in some cases be sufficient without further testing (see section 2.2.1).

### 2.1.1. Technical data

#### 2.1.1.1. Identity and nature of the source material

It is recognized that identification of the botanical source and botanical preparation may in some cases be complicated. It is recommended to follow as much as possible the nomenclature of the European Pharmacopoeia. Additional nomenclature sources are as follows:

World Checklist of Selected Plant Families (Royal Botanic Garden, Kew); the books by Hanelt (2001) also available on the Internet as Mansfeld's World Database of Agricultural and Horticultural Crops; and the database by United States Department of Agriculture. If a scientific name is not found in any of the above-named references, its existence may be checked in The International Plant Names Index.

Since there have been many instances where species have been reclassified or renamed, a same species may be known by different scientific names. Common (vernacular) names may also be provided, but it should be noted that a common name used in one region to refer to a particular plant may be used elsewhere to refer to another quite unrelated species. Hence common names may not uniquely identify a species and are not as reliable as the scientific names.

The following scheme summarizes the requirements for description of the identity of the botanical:

Scientific (Latin) name:	<i>full systematic species name incl. botanical family, genus, species, variety, subspecies, author's name, and chemotype if applicable</i>
Synonyms:	<i>botanical name(s) that may be used interchangeably with the preferred scientific name</i>
Common names:	<i>vernacular name(s)</i>
Part used:	<i>e.g. root, leaf, seed ...</i>
Geographical origin:	<i>continent, country, region</i>
Growth and harvesting conditions:	<i>wild or cultivated, cultivation practices, time of harvest in relation to both season and stage of the plant growth.</i>

#### 2.1.1.2. Manufacturing process

The following information is considered necessary for assessing the safety of botanicals and botanical preparations:

- i) Information on the method(s) of manufacture (e.g. the process by which the raw material is converted into a preparation, such as extraction or other procedure(s), and plant extract ratio)
- ii) Information on substances entering the manufacturing process, e.g. identity of the extraction solvent, reagents, special precautions (light and temperature).
- iii) Standardization criteria (e.g. see European Pharmacopoeia).

Botanicals or botanical preparations might become hazardous as a result of deviations in the production process (e.g. misclassification, switching of species). Therefore the safety of botanicals and botanical preparations should be ensured by following a Hazard Analysis and Critical Control Point (HACCP) approach (Codex Alimentarius 1997). The whole production chain, from primary production of botanicals to the storage and commercialisation of the botanical preparations should be taken into consideration. The HACCP system must be applied with the necessary flexibility and adapted to each botanical preparation on a case-by-case basis.

#### 2.1.1.3. Chemical composition

Data on the chemical composition of the botanical ingredient should be provided with emphasis on the concentrations of constituent of relevance for the safety assessment; this includes the concentrations of:

- Compounds should be classified according to their chemical structure (e.g. flavonoids, terpenoids, alkaloids, etc.). Levels at which the constituents are present in the respective part of the botanical or botanical preparation should be given where available.
- Constituents to characterise the quality, chemical fingerprint, production process and/or biological activity of the preparation (markers).
- Constituents that provide reasons for concern due to their chemical, physiological or toxicological properties.

In some cases, it may be difficult to identify the active principle responsible for an effect. Therefore the strength of the evidence underlying the concerns over a compound being reason for concern should also be given.

#### 2.1.1.4. Specifications

Specifications of the botanicals or botanical preparations are required. They may be based on nutritional or biologically active components or, when these are not known, on selected chemical markers. Limits for or absence of specific undesirable / toxic substances should be specified. The proposed specifications should be modelled on recent European or other internationally accepted specifications (e.g. pharmacopoeia or the guidelines of the EMEA Committee on Herbal Medicinal

Products (HMPC)<sup>15</sup>). Where the proposed specifications differ from internationally recognised specifications, the latter specifications should be set out alongside the proposed new specifications, and any differences pointed out. Validated and well-established methods should be preferably used for the analysis of compounds considered in specifications.

The specifications should include concentrations of major groups of constituents present in the botanical preparation including for example: amino acids, lipids, polysaccharides, volatile oil, inorganic ions, polyphenols, alkaloids, terpenes, alkenylbenzenes, lignin, saponins etc. as well as the major constituents within these classes.

In addition, information on maximum levels for possible contaminants including e.g. heavy metals, mycotoxins, pesticide residues, and polycyclic aromatic hydrocarbon (PAH) residues should be provided.

#### 2.1.1.5. Stability of the botanical or botanical preparation used as ingredient in food supplement

The stability of the botanical ingredient should be demonstrated over the shelf-life time. Any information concerning possible degradation should also be provided.

#### 2.1.1.6. Proposed uses and use levels

Information on intended uses and recommended intakes for a product should specifically mention uses and use levels for the following categories:

- Common foods
- Food supplements
- Medicinal products

Special attention should be given to population groups with specific uses like for example young children. Information on the duration of the proposed uses and use levels should also be provided

#### 2.1.1.7. Information on existing assessments

Information on any existing assessments by international bodies or national competent authorities should be provided.

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<sup>15</sup> See <http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm>, CPMP/QWP/2820/00 Rev 1 and CPMP/QWP/2819/00 Rev 1

### 2.1.2. Exposure: extent and duration

Data and information should be provided on:

- i) Anticipated human exposure to the botanical ingredient, including amount (e.g. maximum and average daily intake or exposure), frequency and duration. It is important to characterize as much as possible the expected human exposure to the botanical ingredient according to the recommended modalities of use in terms of extent and duration. Clear distinction should be made between intake of a botanical itself, intake of its essential oil and other preparations made of it.
- ii) Possibility of additional / combined human exposure to the botanical or botanical preparation through different categories of food, food supplements and/or medicinal products that can be consumed together.
- iii) Modality of use of the ingredient.
- iv) Information on historical (food, food supplement and medicinal) use of the ingredient in human population groups in relation to the modalities of use and resulting exposure levels if known. Data derived from use outside of the European Union should also be considered.

All data should be representative of the ingredient to be used for the European market. In this context, food use includes, in principle, the consumption of raw and cooked vegetables, spices, flavours, food supplements already in use for a long time<sup>16</sup> and any other related food items.

Estimates of average exposure ranges associated with the use of the botanical ingredient in the EU Member States should also be provided. Uncertainties associated with the food consumption data considered and anticipated exposure ranges should be clearly described (EFSA, 2006b).

A matter to be specifically addressed in the evaluation is whether the proposed use and use levels will significantly increase already existing human exposure.

### 2.1.3. Toxicological data

Studies on toxicity and toxicokinetics including metabolism of botanicals and botanical preparations should be conducted using internationally agreed protocols. Test methods described by OECD or in European Commission Directives 87/432/EEC and 67/548/EC – Annex 5 are recommended. It is advisable to ensure that the most up-to-date version of any test guideline is followed. Use of any methods differing from internationally agreed protocols should be justified. Protocols for special studies differing from standard tests should be developed on a case-by-case basis.

To ensure general acceptance of the data submitted, studies should be carried out according to the principles of Good Laboratory Practice (GLP) described in Council Directive 87/18/EEC and accompanied by a statement of GLP compliance. Adequate explanation should be provided for divergence from these principles.

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<sup>16</sup> The time duration of exposure to the botanical ingredient without any reported adverse effect that would allow a presumption of safety depends on a number of different issues, such as levels and modalities of exposure. Therefore, it is not possible to provide a minimum figure for such duration, applicable to all food supplements.

Council Directive 86/609/EEC, on the protection of animals used for experimental and other scientific purposes, requires that care is taken to avoid unnecessary use of animals. Studies carried out should be those necessary to demonstrate the safety of a botanical or botanical preparation and planned in accordance with the principles of reduction, refinement and replacement. However, where adequate data are not available for the safety assessment (see section 3.2.1), *in vivo* studies using experimental animals may be needed in order to assess possible risks to humans from the ingestion of botanicals or botanical preparations. Alternative validated methods involving fewer or no animals for toxicity endpoints may in the future be developed and should be considered on a case-by-case basis.

If available, data on possible interactions (e.g. herbal-drug) should also be provided.

## **2.2. Proposed general framework for assessing the safety of botanicals and botanical preparations used as ingredients in food supplement**

Several guidance documents (AFSSA, 2003; Council of Europe, 2005; Schilter et al., 2003) have been published on the principles for assessment of botanicals and botanical preparations in the food and feed area. The present guidance document is not intended to reiterate these, but to outline a framework that could be used by risk assessors when assessing the safety of a botanical or a botanical preparation. It also proposes a scientific approach to the assessment of available data.

The aim of the assessment is to ensure that botanicals or botanical preparations, when used in food supplements in the manner, quantities and time period of intake proposed, would not pose a risk to the health of consumers. Data should provide not only information relevant to the healthy adult consumer, but also relevant to those population groups potentially vulnerable due to their pattern of food consumption or their physiological or health status, *e.g.* young age, elderly, pregnancy, immunocompromised *etc.*

A general framework for assessing the safety with core tests and other tests is given, which should enable determination of what information is required to establish the safety-in-use of the botanical or botanical preparation. The application of this guidance to specific cases will depend on the nature of the botanical or botanical preparation, its intended uses and levels of use in food supplements and on whether the botanical or botanical preparation has a long term history of food use<sup>17</sup>, showing that, at proposed exposure levels, no adverse effect on human health has been reported. In addition to laboratory tests, it may be possible to use human data derived from medical use, epidemiology, or specific studies on volunteers (e.g. on absorption and metabolism), or any other data reporting possible adverse health effects, either anecdotal or on the basis of case reports of intoxication, e.g. data related to toxicity on livestock animals, or on botanicals that closely resemble botanicals which are known to have caused toxic effects.

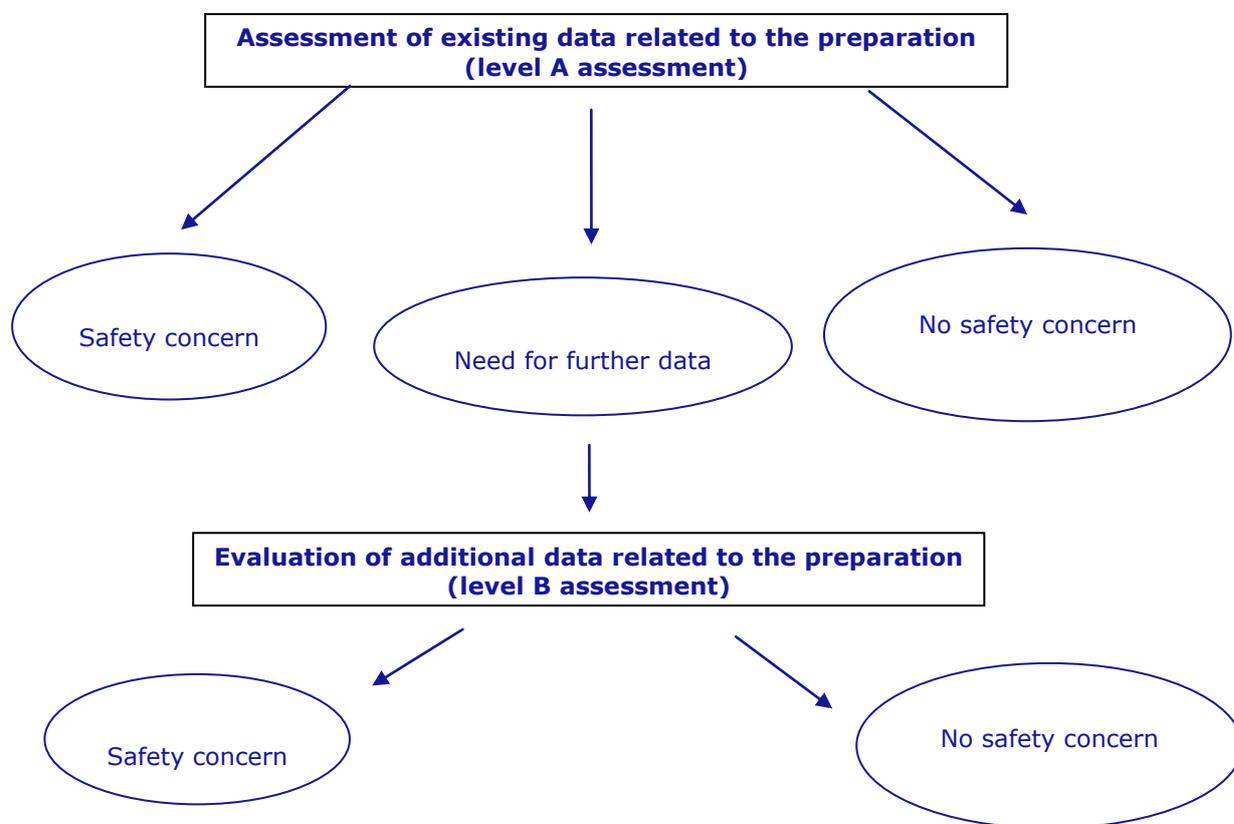
However, it is recognized that for botanical ingredients lacking a history of food use, or for botanicals whose intended use levels will significantly exceed historical intake levels, an assessment of safety generally relies on experimental toxicity data largely derived from investigations in laboratory animals.

The approach herein proposed for the safety assessment of botanicals and botanical preparations not regulated in the framework of specific regulations such as the one on novel foods, and illustrated by Figure 1, consists of the two following levels:

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<sup>17</sup> In this context, history of food use includes human consumption as nutrients, spice, flavourings, appetizer and any other food items. See also footnote 16.

- Level A: Safety assessment based on available knowledge.
- Level B: Safety assessment including newly generated data.



**Figure 1:** Proposed tiered approach for the safety assessment of botanicals and botanical preparations.

### 2.2.1. Level A: Safety assessment based on available knowledge

Depending on the botanical ingredient and its uses, there are circumstances under which no additional data are judged necessary for the safety evaluation, i.e. a presumption of safety would be applied. This would be the case whenever available data would allow to conclude that exposure to known levels of the botanical ingredient has occurred in large population groups for many years without reported adverse effects.

Therefore, an important requirement is that the data as outlined in chapter 2.1 are provided and 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 composition of the botanical preparations should be in line with historically used ones. 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.

If compounds of concern can be well defined, evaluations can focus on these specific compounds. In some cases, it may be difficult to identify the active principle responsible for an effect. In such cases the strength of the evidence underlying the concerns over a compound taken as the reference compound for the safety evaluation should also be given.

For botanicals and botanical preparations with a potential to contain toxic, addictive, psychotropic or other substances that may be of concern (see also the Compendium and section 3), presumption of safety can be applied only if there is convincing evidence that these undesirable substances in the specific plant parts or preparations are either absent in the source material, or significantly reduced if not excluded, or inactivated during processing.

In cases where the above-mentioned substances are known to be present in the botanical ingredient under evaluation (see attached Compendium), additional consideration should be given to support the presumption of safety of the botanical preparation. The significance of overall exposure to such substances should be assessed and compared with existing health-based guidance values such as the acceptable / tolerable daily intake (ADI/TDI). Consideration of exposure to the substance of concern in relation to the Threshold of Toxicological Concern (TTC) values may also be helpful<sup>18</sup>.

In cases where no health-based guidance values are available or where the botanical ingredient contains substances that are both genotoxic and carcinogenic, the “Margin of Exposure” (MOE) approach (EFSA, 2005) could be applied covering the botanical(s) under examination and any other dietary sources of exposure. The MOE approach compares toxic effect levels with human exposure levels. Alternatively, it could be evaluated whether the expected exposure to the genotoxic and carcinogenic ingredient is likely to be increased, compared to the intake from other sources.

It is plausible that the kinetics as well as the expression of the inherent toxicity of a naturally occurring substance could be modified by the matrix in which it is present. Depending on the mechanism of action, this could result in the toxicity being unchanged, reduced or even increased. Research on individual substance/matrix interactions or botanical preparations cannot be used to draw general conclusions about intact botanicals, herbs and spices under all conditions of use, ingestion and metabolism. Where a matrix effect is advocated to support the safety of specific levels of substances (e.g. that data from a pure substance may overestimate effects of the substance in the botanical matrix), testing and/or other data should be provided to demonstrate the occurrence of the matrix effect of the preparation and its magnitude. A matrix effect should be judged on a case-by-case basis.

Extrapolating from one preparation to another and/or from one botanical to another with respect to the same substance of toxicological concern can only be considered when accompanied by evidence of their composition with respect to the substance of concern and pattern of consumption.

For food supplements consisting of complex mixtures of different botanicals, the above-mentioned assessment could be carried out on the levels of individual substances of concern known to be present (see also the Compendium), with the understanding of the limitation that such an approach does not generally allow the assessment of possible synergistic or antagonistic effects. Any data on possible herb-drug interaction should be carefully considered.

In the case of a botanical ingredient whose anticipated intake is significantly higher than the estimated historical intake level, or for which the historical intake level cannot be assessed, additional data should be provided for the safety assessment, as described in the following sections.

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<sup>18</sup> The EFSA Scientific Committee is currently exploring options for the use by EFSA’s Scientific Panels of the TTC approach for providing scientific advice about possible human health risks.

### 2.2.2. Additional data required for the level B assessment

The reasons for carrying out toxicological studies should be stated, as should the reasons for not submitting a study that might be expected. The studies that might be expected can be seen from the “Guidance on submissions for food additive evaluations by the Scientific Committee on Food” (SCF 2001b). All the important results should be presented and discussed and the original study reports should be submitted in order to allow independent, critical appraisal.

The toxicology section of the dossier should start with a section describing in detail the specifications and identity criteria for the botanical preparation(s) used for the toxicity studies and their relationship to the final product to be used in the food supplement. It should be demonstrated unambiguously that these characteristics are in compliance with the technical details specified for the botanical preparation in this report.

The toxicological tests should, as far as possible, follow the recommendations for data reporting given in the relevant guidelines (e.g. OECD, 1998). The material to be tested, with lot or batch number, should be well identified, characterized and standardized. It is important that for each study performed it is stated whether the test material conforms to the proposed specifications. If it does not conform, then the specifications of the test material should be given together with a rationale for using these data in the safety assessment of the product intended for the market.

- Toxicokinetics including metabolism

Information on toxicokinetics of relevant biologically active constituents present in the botanical or botanical preparation should be provided whenever available from the literature. Not all aspects need to be investigated in every case. Additional issues that may deserve consideration are:

- The possibility of interactions among constituents of the botanical or botanical preparation that can alter bioavailability, metabolism, and toxicity.
- The possibility of interactions with medicinal products.

- Genotoxicity testing

For the genotoxicity testing of botanicals and botanical preparations, *in vitro* tests covering effects both at gene and chromosome levels are required<sup>19</sup>. Specific tests are likely to include the Ames test (OECD guideline 471) and an *in vitro* test for the detection of chromosomal aberrations (OECD guideline 473) or an *in vitro* micronucleus assay (draft OECD guideline 487), and possibly the mouse lymphoma tk assay (OECD 476). The particular test strategy may depend upon the test material considered.

There may be circumstances under which it may be justified to deviate from the above-mentioned core set. In such cases a scientific justification should be provided and additional types of considerations or mechanistic studies may be needed.

A positive *in vitro* test normally requires follow-up by *in vivo* testing, unless it can be adequately demonstrated that the positive *in vitro* findings are not relevant for the *in vivo* situation. The choice of

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<sup>19</sup> The EFSA Scientific Committee has been requested by EFSA to review the current state-of-the-science and provide recommendations on genotoxicity testing strategies, which could contribute to greater harmonisation between EFSA Panels on approaches to such testing.

the appropriate *in vivo* test is critical, due to different sensitivities, different endpoints and other variables. It requires expert judgement based on all available information, to be applied case-by-case. For this reason, a flexible approach is preferable to a fixed decision tree.

- Subchronic toxicity testing

A 90-day study in the rat with the test material administered via the diet is the minimum requirement to establish a no-observed-adverse-effect level. Subchronic toxicity testing should be carried out independently of the results of the *in vitro* and *in vivo* genotoxicity testing.

- Other studies

Depending on the outcome of the genotoxicity and subchronic toxicity studies, or other specific relevant information, further studies may be required (e.g. reproductive toxicity, developmental toxicity, neurotoxicity, immunotoxicity, chronic toxicity/carcinogenicity).

### **3. Establishing a Compendium of botanicals and prioritising them to be considered for a safety assessment.**

A Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances that may be of concern has been produced to complement the present guidance document.

The Compendium contains the following information:

- The botanical (binomial) denomination of the plant (genus, species and in some cases variety or subspecies when relevant), with synonyms in use.
- The plant parts and substances of possible toxicological concern
- Additional specific information of relevance for the risk assessment, e.g. adulterations
- References, either to existing international / national list of plants that were used to populate the Compendium, or to published literature when specific information has been added.

The Compendium aims at flagging plants or part of plants or substances of possible concern for human health naturally present in the listed botanicals and that, therefore, require specific attention while assessing the safety of the product(s) containing such botanical(s). For some botanicals in the Compendium, adverse (toxic) effect(s) are mentioned although sometimes based on anecdotal reports and even though the constituent(s) of concern are not elucidated in the literature. In some cases the whole genus was flagged because of the likely presence of substances of concern characteristic for the toxicity of that genus.

The presence of a substance of concern in a given botanical does not mean that this substance will also be present in the botanical preparation. This depends largely on the plant part used, as well as the preparation method.

The Compendium contains also an “insufficient information” list regrouping botanicals that appear in one of the sources of information, but for which sufficient information could not be found on possible substances of concern, or for which the information available could not be verified.

Without prejudice to the existing legal framework, it should be noted that this Compendium has no legal status and should not be used as support or evidence in any disagreement or dispute pertaining to the legal classification of products or substances.

The Compendium is a living document which should be periodically updated by EFSA. As a consequence, the absence of a given species in this Compendium cannot be interpreted as meaning that the species is devoid of substances hazardous for human health. In the same way, not mentioning a specific part of plant, does not imply absence of substance(s) of concern in this part. Botanicals that have not been reported as having been considered for food or food supplement use in the European countries or botanicals classified as novel foods or GMOs will not appear in the Compendium.

**Priority setting for safety assessment:**

The botanicals in the above-mentioned Compendium should be assessed according to the following recommendations:

Priority should be given to botanicals and botanical preparations:

- known to have an established history of food use and that have been identified to contain significant levels of substances of concern.
- that are not allowed/recommended for food use in some European countries, but which are still in use in some other EU countries, particularly when the intended use levels in food are known or expected to be high.
- for which some adverse health effects have been reported, either anecdotally, or on the basis of case reports of intoxication, epidemiological data or any toxicity data from livestock animals or experimental animals, or for botanicals that closely resemble botanicals which are known to have caused toxic effects.
- for which consumption has significantly increased during recent years in Member States.
- for which there are both limited history of use and toxicity data available, and for which the intended use levels are expected to be relatively high (e.g. high interest to the food industry).

Botanical ingredients that are reported to have a low toxic potential, and for which the intended intake/exposure levels are within the range of intake levels resulting from the European Member States average diet would be given a low priority.

## CONCLUSIONS AND RECOMMENDATIONS

A two-level tiered approach for the safety assessment of botanical ingredients intended for use in food supplements is proposed. This approach consists of a safety assessment based on available knowledge and a subsequent level in which further testing and/or data are required. It allows the recognition of presumption of safety without further testing, based on long-term history of use with no reported adverse effect and with no significant increased exposure. For those botanical ingredients for which a presumption of safety based on available data cannot be established, it introduces a framework for assessing their safety, including the types of testing that would be most useful. Recommendations for prioritising botanicals for safety assessment are also made.

The Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances that may be of concern, is considered to facilitate the assessment by flagging possible safety issues, and should therefore be considered as an essential part of this guidance document. The Scientific Committee recommends to maintain it up-to-date, making use of relevant available national lists of plants and of any other relevant data available, as well as of updated assessments carried out on botanicals by qualified bodies. The Scientific Committee also recommends to further expand the Compendium with botanicals not having any market history in Europe in order to prepare the implementation of the new Novel Food Regulation, which foresees a notification process for botanicals and botanical preparations having a history of safe use in the third country of origin.

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**Discussion Paper on “Botanicals and Botanical Preparations widely used as food supplements and related products: Coherent and Comprehensive Risk Assessment and Consumer Information Approaches”**

(adopted by written procedure on 23 June 2004)

1. In view of the fact that botanicals and botanical preparations intended for human consumption as food supplements and related products are very widely marketed with a variety of claims, the present discussion paper aims at increasing awareness of some key issues to improve comprehensiveness and coherence of current approaches to risk assessment and consumer information on these products \*.
2. A large number of botanical materials (e.g. whole, fragmented or cut plants, algae, fungi, lichens), and botanical preparations obtained from these materials by various processes (e.g. extraction, distillation, purification, concentration and fermentation) readily find their way onto the food supplements market. These materials are also often labelled as natural foods, largely organic, and foods specifically intended to support sport activities. Personal care products and the so-called “traditional herbal medicinal products” represent additional sources of exposure of consumers to botanical products. New products are also emerging, consisting of substances that commonly occur at low levels in botanical components of the diet, which are then extracted and re-introduced at much higher levels in specific products.
3. Botanicals and botanical preparations are widely available to consumers through several distribution channels in the E.U. and elsewhere. In particular, they are sold over the counter in pharmacies and can be bought in supermarkets, herbalist’s shops and other shops, or via the Internet. They are currently available and used in such a way that they are almost becoming part of the common diet, thus providing for a significant human exposure from a public health point of view.

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\* The use of botanicals and botanical preparations intended for animal consumption is not dealt with in this paper.

4. There are some general concerns with respect to botanicals and botanical preparations mainly relating to quality and safety issues:
  - Contamination (both chemical and microbiological) is a documented problem. It has been associated, for example, with botanical products originating from Asia. Deaths through poisoning following consumption of such products have been reported in Europe and the US arising from contamination with heavy metals, synthetic drugs and other undesirable substances (Ernst, 2002). Misidentification of plants harvested from the wild is also a continuing problem. When sales of traditional herbal products remained restricted to particular ethnic groups, which are familiar with the products and able to exert a local control on quality, problems were more rarely encountered. The growing volume of sales in the European Union with products obtained from suppliers based in Asia or elsewhere and the move towards widespread outlets for the products of traditional medicine call for more formal pre-marketing assessment and more stringent controls than the occasional random checks and analyses often carried out by individual national or local authorities on what is already out in the market.
  - There is world-wide recognition of potential problems associated with botanicals and botanical products, not only in terms of safety, but also in terms of the claimed amounts and stability of the active ingredients. For example, the US Pharmacopeia, which considers the safety of food supplements as well as medicines, announced in December 2002 the establishment of an advisory panel specifically to advise on improving the quality of botanical products.
  - Any efficacy shown by botanical products is usually a product of one or more plant secondary metabolites. Secondary metabolism responds to stress imposed by biotic and abiotic factors and, as a consequence, patterns and concentrations of metabolites can show considerable variation among plants belonging to the same species and variety. For instance, it is not unusual for metabolites produced in response to pathogen attack to vary in concentration one thousand-fold over short time periods. While consistency of product is more easily controlled in cultivated plants, particularly those grown in containment, collections from the wild make it difficult to ensure that concentrations of bioactive agents meet specifications and are within safe limits.
  - A very large literature exists on toxic substances naturally-occurring in plants. Of particular concern are plant products consumed in concentrated forms. Concerns can relate directly to the toxicological profile of the active agent(s). It has been the case with kava-kava (*Piper methysticum*), its withdrawal from the market being advised recently because of the association of its consumption

with acute liver failure (Kraft *et al.*, 2001). In June 2001, the US FDA, following action by the UK and Australia, advised manufacturers of dietary supplements to avoid the use of the various types of comfrey (*Symphytum* spp.) because of the health concerns associated with the presence of pyrrolizidine alkaloids. Moreover, since 1993, cases of nephrotoxicity and carcinogenicity have been reported in Belgium, France and United Kingdom as a result of inadvertent exposure to *Aristolochia* species in unlicensed herbal medicines (EMEA, 2000).

- Interactions of herbal products with prescription products are well recognised, although widely under-reported (Ernst, 2000; Sorensen, 2002). In the past, when such products were usually obtained from outlets run by knowledgeable individuals, advice on use and contra-indications was often available. Currently, contra-indications do not usually appear on the labels or any associated documentation when herbal products are sold through supermarkets and other retail outlets. Yet, a survey of the available information on interactions with medicinal compounds of the more commonly purchased botanical products (e.g. ginkgo, garlic, St. John's Wort and ginseng) found recorded adverse interactions for all but *Echinacea* and saw palmetto (Izzo and Ernst, 2001). Incidence and severity of effects associated with prescription drug-dietary supplement interactions in a small group of primary care patients have also been investigated by Peng *et al.* (2004); the most common botanical products included garlic, ginkgo biloba, saw palmetto and ginseng. While most interactions were judged not to be serious, an incidence of 6% of potentially severe health consequences was recorded among patients taking at the same time specific drugs and specific botanical products.
5. This heterogeneous group of commodities includes products which, mainly depending on their intended uses and presentations, fall under different Community regulatory frameworks and for some types of products legal provisions for a preliminary risk assessment do not exist yet. The main legislations to be considered in this context are Directive 2002/46/EC on food supplements and Directive 2004/27/EC on traditional herbal medicinal products:
- Directive 2002/46/EC foresees the use as food supplements of vitamins and minerals listed in the Annexes to the Directive. It also allows the use for the same purpose of still undetermined substances with a nutritional or physiological effect, but definition of such effects is not provided for. According to Art. 4, para 8, the European Commission shall produce, not later than 12 July 2007, a report on the advisability of establishing specific rules, including, where appropriate, categories of additional vitamins and minerals or of substances with a nutritional or physiological effect, accompanied by any

proposals for amendments to Directive 2002/46/EC<sup>\*\*</sup>. Thus a regulatory framework for further developments in this area already exists.

- Directive 2004/27/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 a simplified registration procedure, based on “traditional use”, but ensuring quality and safety as for any other medicinal product. Community lists will have to be prepared of traditional herbal medicinal products, herbal preparations and herbal products. On the other hand, traditional herbal materials, which are authorised for use in medicinal products, will continue to contribute to the dietary intake of bioactive agents as long as they comply with the general food regulations and make no medicinal claim.
6. Also relevant in this context are the Directives 1989/398/EEC and 96/84/EC on “Food for special purposes” and the Regulation 1997/258/CE on “novel foods” that provide additional channels for some botanicals and botanical preparations to enter the food market, and the proposed Directives on “nutritional and health claims” and “food fortification” at present under consideration by the European Parliament and Council.
  7. As the market volume expands, so does the need for a better characterisation of botanicals and botanical preparations, and for harmonising the scientific assessment of risks from exposure of consumers to these products.
  8. It is important, therefore, from a public health point of view, to achieve a comprehensive and coherent approach to risk assessment and consumer information on botanicals and botanical preparations widely present in different categories of commodities. Such an approach would, in time, overcome the existing information gaps on many of these products and bring together the fragmentary provisions for risk assessment on botanicals and botanical preparations in the current relevant regulations. To this end, the present paper aims at increasing awareness on these issues and at facilitating a critical analysis of the present situation. It is intended to lead to a stronger partnership and collaboration among all the stakeholders who have a role in this important sector.
  9. Although it is not the objective of this discussion paper to provide a detailed analysis of the way forward, the following reflections address some issues in order to facilitate an open discussion particularly in the frame of future developments of the above-mentioned Directive 2002/46/EC:

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<sup>\*\*</sup> The EC Scientific Committee on Food (SCF) has provided a number of opinions in support of existing and planned legislation on certain aspects of food supplements, and this work is being continued in the relevant EFSA Panels (see [http://europa.eu.int/comm/food/fs/sc/scf/outcome\\_en.html](http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html)).

- As systematic information about the range of botanicals and botanical products present on the market is lacking, consideration could be given, to carrying out a survey to identify the main product categories currently marketed and a study to clarify the potential health-related issues that may need to be addressed.
- In view of the difficulty of compiling a full inventory of botanicals and botanical products, the possibility could also be considered of adopting and regularly updating a list of plants or parts of plants which should not be used or could be put under scrutiny because of the presence of undesirable substances, especially if effective reduction or removal of such substances can not be ensured.
- As purity specifications for all botanicals and botanical preparations are very difficult to define, the development of *ad hoc* manufacturing guidelines, could be considered in order to improve their characterisation and safety. Experience already existing in the pharmaceutical sector could be helpful to this end.
- Considering the importance of providing to consumers adequate information to allow the safe use of botanicals and botanical preparations, the possibility of establishing accredited information sources easily accessible to consumers on these products also deserves attention. A complicating issue in this respect is the diffusion of misleading claims which are very difficult to counterbalance by means of reliable consumer information. However, in this respect, the situation is likely to improve when the proposal for a Community Directive providing for a clear evaluation procedure of “Nutritional and Health Claims” will be adopted.

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