



## **Guidelines for the Registration under REACH of Natural Complex Substances (NCS) used as cosmetic ingredients**

**20 March 2009**

### **1. Preamble**

#### **1.1 Scope**

The REACH Regulation<sup>1</sup> requires the registration of substances manufactured or imported in quantities of 1 tonne or more per year per manufacturer or importer.

Under REACH, a substance is defined as a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

In the European Chemicals Agency (ECHA) Guidance for identification and naming of substances under REACH (June 2007), a distinction is made between substances of well-defined composition and substances that are “of unknown or variable composition, complex reaction products or biological materials” (UVCB).

UVCB substances cannot be sufficiently identified by their chemical composition because:

- the number of constituents is relatively large and/or
- the composition is – to a significant extent – unknown and/or
- the variability of composition is relatively large or poorly predictable.

Consequently, UVCB substances require other types of information for their identification, in addition to what is known about their chemical composition.

Natural and complex substances (NCS) are a subgroup of UVCB substances which have important uses in cosmetics and other consumer products. They are complex substances occurring in nature that can be of various origins (botanical, animal, mineral or biotechnological). NCS of botanical origin cover the largest number of the NCS used as ingredients in cosmetics and in other consumer products.

Some general examples of NCS are given in Annex I. Single identified molecules and polymers (when the latter fall under the definition in Article 3.5 of the REACH Regulation) are outside the scope of this document.

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<sup>1</sup> REACH: Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006. Off. J. of the European Union L396/1 of 30-12-2006. [http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l\\_396/l\\_39620061230en00010849.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_396/l_39620061230en00010849.pdf)

Specific methodology has also been developed by industry<sup>2</sup> for the registration under REACH of NCS used as fragrance ingredients. Whilst fragrance NCS are not covered by the scope of the present document, the principles presented here do not exclude them and will apply, wholly or partially, to those NCS where appropriate.

### **1.2 Objective of this document**

The objective of this document is to present an approach suitable for the registration under the REACH Regulation of NCS, taking botanicals and botanical extracts as example. These include but are not limited to:

- Botanicals (plants, seaweeds, and fungi) as such,
- Botanical extracts,
- Botanical extracted fractions.

Botanical extracts are substances obtained by the action of appropriate solvents and processes on a fresh or dried plant, or part of a plant. These extracts can be further processed to select or to eliminate part of the constituents and to obtain plant extracted fractions.

Botanicals and botanical extracts are specific categories of NCS of botanical origin used as ingredients in cosmetics and other types of consumer products

In addition to the NCS of botanical origin, some other substances present the same characteristics as the botanicals and botanical extracts that are subject to this document:

- o biotechnological substances;
- o animal extracts and derivatives;
- o derivatives from minerals or mineral soils.

For these NCS of biotechnological, animal or mineral origin, the methodology proposed in the present document for botanical NCS can apply with relevant adaptations, in particular in the field of substance identification.

Even if other methodologies can be applied in some specific cases, those provided in this document and in "The registration for REACH of Natural Complex Substances used as fragrance ingredients", cover the largest majority of NCS present in cosmetic products.

The presented approach takes into account the objectives of REACH and the special nature of these materials and is the result of the joint efforts of the producers and downstream users<sup>3</sup> of these NCS.

### **1.3 Overview of REACH legislation and ECHA Guidance relevant to NCS**

The unique situation of NCSs was recognised during the development of REACH. Provisions for the registration of these substances have been made in the following sections of the final REACH text and in the relevant ECHA guidance documents:

1) Recital 35: The Member States, the Agency and all interested parties should take full account of the results of the RIP<sup>4</sup>s, in particular with regard to the registration of substances which occur in nature.

2) Recital 45: The European Inventory of Existing Commercial Chemical Substances (EINECS) included certain complex substances in a single entry. UVCB substances (substances of unknown or variable composition, complex reaction products or biological materials) may be registered as a single substance under this Regulation, despite their variable composition, provided that the hazardous properties do not differ significantly and warrant the same classification.

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<sup>2</sup> The European Cosmetics Association (COLIPA), the International Association for Soaps, Detergents and Maintenance Products (AISE), the International Fragrance Association (IFRA) i.e. the global association, the European Flavour and Fragrance Association (EFFA), one of its members, the European Federation of Essential Oils (EFEO), the International Federation of Essential Oil and Aroma Trade (IFEAT), the European Organization for Cosmetic Ingredients Industries and Services (UNITIS), and the European Herb Growers Association (EUROPAM), L'Office National Interprofessionnel des Plantes à Parfum, Aromatiques et Médicinales (Onippam): The registration for REACH of Natural Complex Substances used as fragrance ingredients, 29 August 2007.

<sup>3</sup> The European Cosmetics Association (COLIPA), the European Organization for Cosmetic Ingredients Industries and Services (UNITIS), and the European Federation of Essential Oils (EFEO).

<sup>4</sup> RIPs : REACH Implementation Projects coordinated by the European Commission and involving relevant stakeholders.

3). Article 3 “Definitions”: paragraphs 1 (substance: see definition on page 1), 39 (substance which occurs in nature: naturally occurring substance as such, unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation, by extraction with water, by steam distillation or by heating solely with water, or which is extracted from air by any means), and 40 (not chemically modified substance: a substance whose chemical structure remains unchanged, even if it has undergone a chemical process or treatment, or a physical mineralogical transformation, for instance to remove impurities).

4). Article 138.4: The Commission shall carry out a review of Annexes I, IV and V by 1 June 2008, with a view to proposing amendments, if appropriate, to them in accordance with the procedure referred to in Article 131.

5). Annex IV: exemptions from the obligation to register, as sufficient information is known about these substances as they are considered to cause minimum risk because of their intrinsic properties.

6). Annex V: exemptions from the obligation to register, as registration is deemed inappropriate or unnecessary for these substances.

Annex V, paragraph 7: The following substances which occur in nature, if they are not chemically modified: minerals, ores, ore concentrates, raw and processed natural gas, crude oil, coal.

Annex V, paragraph 8: substances which occur in nature other than those listed under paragraph 7, if they are not chemically modified, unless they meet the criteria for classification as dangerous according to Directive 67/548/EEC or unless they are persistent, bioaccumulative and toxic or very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII or unless they were identified in accordance with Article 59(1) at least two years previously as substances giving rise to an equivalent level of concern as set out in Article 57(f).

Annex V, paragraph 9: the following substances obtained from natural sources, if they are not chemically modified, unless they meet the criteria for classification as dangerous according to Directive 67/548/EEC with the exception of those only classified as flammable [R 10], as a skin irritant [R 38] or as an eye irritant [R 36] or unless they are persistent, bioaccumulative and toxic or very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII or unless they were identified in accordance with Article 59(1) at least two years previously as substances giving rise to an equivalent level of concern as set out in Article 57(f): vegetable fats, vegetable oils, vegetable waxes; animal fats, animal oils, animal waxes; fatty acids from C<sub>6</sub> to C<sub>24</sub> and their potassium, sodium, calcium and magnesium salts; glycerol.

7) Annex XI, section 1.5 on Grouping of substances and read-across approach (last sentence): The agency, after consulting with relevant stakeholders and other interested parties, shall issue guidance on the technically and scientifically justified methodology for the grouping of substances sufficiently in advance of the first registration deadline for phase-in substances.

8) ECHA Guidance on QSARs and Grouping Of Chemicals, May 2008, addresses the special situation of NCS and concludes that inclusion in a chemical group is possible based on the constituents of the NCS where the major components can be clearly identified as the same as known chemical substances. However, it does not take into account the variations in composition and the high number of registrations that would be resulting from these variations.

9) ECHA Guidance for identification and naming of substances under REACH ([http://guidance.echa.europa.eu/docs/guidance\\_document/substance\\_id\\_en.pdf](http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.pdf)) includes a specific guidance for the identification and characterization of UVCB substances. Whilst important, this does not sufficiently address all the specific problems that the variability and complexity of these substances pose for their registration under REACH, as illustrated by the historical positioning of the different variants and qualities of NCS originating from the same botanical species under one EINECS identification.

## 2. Unique technical and physical aspects of NCS used as ingredients in cosmetics and other consumer products

The following facts about NCS of botanical origin make them a unique class of UVCBs with regard to REACH:

- a) Their composition is most often very complex. For example, *Calendula officinalis* – Marigold – extracts can contain more than 150 components.
- b) Being natural products, there are natural variations in the chemical composition of NCS of botanical origin as a consequence of:
  - the region of growth
  - the annual variations in climate within the region
  - the variations between botanical species of the same family
  - the part of plant used
  - the methodologies for primary processing such as drying, cutting, etc.
- c) Their composition is dependant of the methodologies used for processing such as expression, extraction, fractionation, concentration, etc.
- d) The vast majority of plants from which botanical NCS cosmetic ingredients are obtained, have been used for centuries as components of skincare or topical medicinal products. They have a long history of safe use.

As a result, and if the current status is retained, REACH registrations will have to manage many different qualities of NCS of botanical origin even when they are derived from the same botanical species.

A Classification of NCS in general, and of botanical NCS in particular, is proposed and annexed to the present document – see Annex 1.

## 3. Hazard Classification of NCS

The majority of botanical extracts to be registered is incompletely characterized and consists of a large number of constituents, part of which are unidentified.

However, Annex I of the European Dangerous Substances Directive (DSD, 67/548/EEC) provides the list of the substances that are classified as dangerous as well as the conditions according to which a complex substance containing a dangerous substance may have to be classified as dangerous itself.

The new Regulation on the Classification, Labelling and Packaging of Dangerous Substances and Mixtures (CLP, (EC) 1272/2008), which entered into force on 20 January 2009, and which will replace the DSD after a transitional period, also specifies these conditions.

In the absence of tests enabling to demonstrate that the NCS does not meet the criteria for classification as dangerous, it will be necessary to show that it does not contain dangerous constituents at levels which may trigger classification of the NCS as dangerous, i.e. above the threshold mentioned in the regulation. This can be done by demonstrating, where relevant, that:

- the concerned plants do not contain dangerous constituents or
- the manufacturing process eliminates or destroys the dangerous constituents possibly contained in the initial botanical, or
- the botanical extract itself does not contain dangerous constituents.

## 4. Proposal for a REACH registration approach for NCS

Given the complexity and variability in composition of botanicals and their extracts described above, a better adapted approach is proposed in order for companies to comply with the requirements of REACH.

The majority of botanicals and botanical extracts to be registered being incompletely characterized and consisting of a large number of constituents a part of which are unidentified, this approach leads to a REACH compliant registration for NCS of botanical origin which would be mainly supported by:

- Identification/Characterization of the NCS with the aim to:
  - Minimize variability
  - Secure traceability
  - Control a reproducible quality
  - Support the safety assessment
- Data from tests conducted on a representative quality of the botanical NCS as such without considering the identified carrying solvent or other carrier.
- Data indirectly obtained by read-across from data on substances or categories of substances related to major constituents or categories of constituents

Registrants of botanical extracts would have to determine which approach (or combination of approaches) is most appropriate on a case-by-case basis.

A REACH registration dossier for botanicals and botanical extracts would consist of:

### 4.1 Identification<sup>5</sup>

- **Substance designation**
  - Trade name and/or Internal Code / Reference, where relevant
  - Common name
  - EINECS number
  - CAS number when relevant
- **Botanical Identity**
  - Scientific name: genus, species with author's name, botanical family, variety or chemotype if relevant.
  - Part of plant used.
- **Origin and Traceability**
  - Geographical origin(s) of the plant
  - Growth and harvesting conditions:
    - . Wild or cultivated: - If wild, evidence of botanical identity such as acceptance after sampling
    - If cultivated, evidence of botanical identity such as origin of seeds or seedling
    - . Time of collection or harvesting in relation to both season and stage of the plant growth
    - . Collection or harvesting practices: preferably according Good Agricultural and Collection Practices – GACP – Supplier's letter of engagement
    - . Pre and post harvest phyto-sanitary treatments including use of pesticides

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<sup>5</sup> The rules chosen for identification are in line with the Draft Guidance Document of the Scientific Committee of EFSA (the European Food Safety Authority) regarding the safety assessment of botanicals and botanical preparations (intermediate document adopted and submitted to public consultation on 19 November 2007) – see Annex 3.

- Description of primary processing: drying, crushing, etc...
- Storage conditions
- Transport conditions
- Control and identification at reception with adapted methods
- **Process**
  - Solvent(s) used
  - Characteristic steps of the extraction process
  - in-process and final controls
- **Specifications**
  - Physical and chemical parameters:
  - Analytical controls through adapted methods:
    - Main significant components of the extract or fingerprint
    - Identified toxicologically significant components, if potentially present at a level of concern
    - Possible contaminants
- Stability data

Examples of how NCS of botanical origin can be identified are provided in Annex 4.

#### **4.2 Representative sample**

Considering the natural variations of the composition of botanicals and botanical extracts, the tests requested by REACH have to be performed on a representative quality of the NCS to be registered. The fact that the quality is representative can be demonstrated by testing a sufficient number of individual batches, or a blend of several batches.

The solvent / other carrier are not part of the sample. Practical guidance for removing the solvent / carrier is provided in Annex 2.

#### **4.3 Physico-chemical, toxicological and ecotoxicological data**

REACH aims to achieve a high level of protection of human health and of the environment while limiting the need for additional testing. One of the key principles in order to meet this objective is that all available data on the toxicological properties of a substance must firstly be evaluated. This principle also applies to NCS. However, due to their complexity, it should be stated that the need to initiate additional toxicological testing for an NCS will closely depend on both its degree of characterisation and its history of use as a foodstuff, food component, cosmetic ingredient or drug.

##### 4.3.1 Physico-chemical data

Due to the characteristics of the NCS concerned by this document, their physico-chemical parameters cannot be standardized and should be adapted to each type or form of substance. Moreover, some methods recommended by REACH are not directly applicable for all types and forms of NCS.

In such a context, data supplied will have to comply with the requirements of the REACH Regulation each time it is relevant and, in case physico-chemical parameters or methods required by REACH are not adapted to the substance, justification of missing data will have to be provided.

Moreover, the attention is especially focused on parameters that are important to determine the toxicological and ecotoxicological properties for their contribution to the overall risk assessment:

- Water solubility, for which the WAF – Water Accommodated Fraction – methodology is recommended for the preparation of the solution while the mass or carbon content dissolved in solution would be used to estimate the solubility
- Partition coefficient – log Pow. Not directly applicable. The shake flask method (octanol/water) could be used
- Vapour Pressure or other parameters related to volatility such as boiling point if adapted.

#### 4.3.2 Toxicological data

Before embarking on animal testing, use of all other available data either on the NCS itself or on its constituents must be considered. In many cases the information gathered may consist of actual test data. However, other types of information may also be sufficient, especially when used in a *Weight of Evidence* approach. Such information could include human data, data from *in vivo* or *in vitro* studies that have not been generated in accordance with the latest adopted/accepted version of the corresponding (validated) test method or to GLP (or equivalent) and / or SAR model outputs, including read-across and category approaches.

Regarding the history of use of some NCS, the concept of similarity and substantial equivalence, that is already used by regulatory authorities such as European Food Safety Authority (EFSA) in the assessment of novel foods and novel food ingredients could also be used in the safety assessment of NCS in the context of the REACH Regulation.

Obviously, the use of existing data prior to initiating experimental studies should lead the assessor to accurately evaluate *data quality* which includes assessment of *adequacy* of the information for hazard/risk assessment and furthermore the two basic elements of *relevance* and *reliability*.

Finally, where available data are not adequate to meet the requirements of the REACH Regulation, additional testing may need to be considered.

Table 1 contains the toxicological end-points for which data is required by REACH, according to the relevant tonnage bands.

**Table 1:**

REACH Annex	Toxicological End-Point	Standard REACH Requirement		
		VII >1	VIII >10	IX >100
<b>Volume (t/y)</b>				
<b>Toxicological information</b>				
8.1	skin irritation/corrosion	x	x	x
8.1.1	skin irritation in vivo		x	x
8.2	eye irritation	x	x	x
8.2.1	eye irritation in vivo		x	x
8.3	skin sensitisation	x	x	x
8.4.1	in vitro gene mutation in bacteria	x	x	x
8.4.2	in vitro cytogenicity study in mammalian cells		x	x
8.4.3	in vitro gene mutation in mammalian cells		x	x
8.5.1	acute oral toxicity	x	x	x
8.5.2	acute inhalation toxicity		x	x

REACH Annex	Toxicological End-Point	Standard REACH Requirement		
		VII	VIII	IX
Volume (t/y)		>1	>10	>100
<b>Toxicological information</b>				
8.5.3	acute dermal toxicity		x	x
8.6.1	short-term repeated dose toxicity study (28 d)		x	x
8.6.2	sub-chronic toxicity study (90 d)			x
8.7.1	screening for reproductive/development toxicity		x	x
8.7.2	pre-natal developmental toxicity study		x	x
8.7.3	two-generation reproduction toxicity study			x
8.8.1	assessment of toxicokinetic behaviour		x	x

#### 4.3.3 Ecotoxicological data

The composition of the NCS of botanical origin introduces a complexity in the determination of ecotoxicological properties which is not encountered for mono-constituent and multi-constituent substances or well-defined complex substances (i.e. complex mixtures which are analytically characterized to at least 90 % w/w).

As a consequence, the application of the standard testing protocols to a NCS of botanical origin can be problematic. Differences in solubility, volatility and other physico-chemical properties of the individual constituents can complicate testing and the meaning of the results. Potential problems with standard test procedures are:

- Differences in partitioning behavior and water solubility between constituents can make it difficult to achieve a homogeneous solution (e.g. if some constituents are highly insoluble in water).
- Some constituents may have individual properties that require steps to be taken to control losses. For example, volatile constituents may require the use of sealed vessels and a minimum headspace
- Multiple constituents may make analytical monitoring impossible or not relevant. For example, it might not be possible to select marker constituents representative of the NCS for this monitoring.
- Interpretation of toxicity results may be difficult. For example, it might not be possible to know which constituents have caused any observed adverse effects.

**Table 2** contains the ecotoxicological tests required by REACH according to the relevant tonnage bands and recommends adaptation of the standard requirements for NCSs of botanical origin from the perspective of their technical feasibility.

Table 2:

REACH Annex	Environment	Adaptation of the Standard REACH Requirement needed ?	VII	VIII	IX
<b>Volume (t/y)</b>			≥ 1	≥ 10	≥ 100
<b>Ecotoxicological information</b>					
9.1.1.	Short-term toxicity test on <i>Daphnia</i>	Yes	x	x	x
9.1.2.	Growth inhibition test on algae	Yes	x	x	x
9.1.3.	Short-term toxicity test on fish	Yes		x	x
9.1.4.	Activated sludge respiration inhibition test	No		x	x
9.1.5.	Long-term toxicity test on <i>Daphnia</i>	Yes			x
9.1.6.	Long-term toxicity test on fish	Yes			x
9.2.1.1.	Biotic degradation (ready biodegradation test)	Current test not feasible	X	x	x
9.2.1.2.	Simulation test on ultimate degradation in surface water	Current test not feasible			x
9.2.1.3.	Soil simulation test	Current test not feasible			x
9.2.1.4.	Sediment simulation test	Current test not feasible			x
9.2.2.1.	Abiotic degradation (hydrolysis = f(pH))	Current test not feasible		x	x
9.2.3.	Identification of degradation products (biotic and abiotic)	Current test not feasible			x
9.3.1.	Adsorption/desorption screening test	Current test not feasible		x	x
9.3.2.	Bioconcentration in fish	Current test not feasible			x
9.3.3.	Adsorption/desorption on soils	Current test not feasible			x
9.4.1.	Short-term toxicity on earthworms	No			x
9.4.2.	Effects on soil micro-organisms	No			x
9.4.3.	Short-term toxicity on plants	No			x
9.4.4.	Long-term toxicity on earthworms	No			
9.4.6.	Long-term toxicity on plants	No			
9.5.1.	Long-term toxicity test on sediment species	Yes			
9.6.1.	Long-term or reproduction toxicity test on birds	No			
<b>Other information</b>					
10.	Methods of detection and analysis	Yes			x

The ecotoxicological properties can be assessed from the data on the NCS or data on the known constituents or structurally related substances and by extrapolation to their concentrations in a typical quality of the NCS following the generally adopted non -testing methods, e.g. those described in the ECHA Guidelines on Information Requirements and on Chemical Safety Assessment. For example, data indirectly obtained by read-across from data on substances or categories of substances related to constituents or categories of constituents can be used for ecotoxicological assessments.

Tests for the purpose of the assessment of these NCSs shall be preceded by an exposure assessment of the identified uses, which may or may not indicate the need for further data for the Chemical Safety Report (CSR).

9.1.1./2./3. NCSs of Botanical origin being complex mixtures of components with variable physico-chemical properties (water solubility, volatility, stability, adsorption ...) create special difficulties with the present test protocols which will require adaptation (e.g. use of the Water Accomodated Fraction – WAF - procedure to prepare test solutions, particular analytical investigations).

Recommendations to make adaptations to the standard testing protocols in aquatic medium are described in OECD (2000) <sup>6</sup>.

As the concentrations should be maintained in test solutions throughout the duration of the test the short-term study on fish should preferably be undertaken under semi-static or flow-through conditions. Under semi-static conditions test solutions are renewed at periods (usually after 24 hours) during the study, while under flow-through conditions test solutions are continuously renewed. This renewal can also prevent the decrease of dissolved oxygen below the accepted level (e.g. 60% of the saturation value). This unexpected decrease test solutions can particularly be observed when the substance represents a good substrate for aerobic micro-organisms.

If all the constituents of the NCS are not fully soluble in the medium across the range of test concentrations, the WAF methodology should be used to prepare test solutions (see § 4.3.1. for determination of water solubility). If the substance is poorly water soluble (< 1 mg/l), the long-term toxicity studies on *Daphnia* and fish (according to Annex IX) may be considered. A sealed system with minimum headspace (for preparation of test solutions and testing) may be required to address volatility.

A specific analytical monitoring is required to demonstrate attainment of equilibrium in preparation of WAF solutions and stability during the test. Marker constituents representative of the NCS can be selected for this purpose. Otherwise a method capable of identifying gross changes in the composition of WAF solutions with time is required. For example, total peak area or dissolved carbon content analysis may be used in monitoring any increases or losses of NCS constituents during preparation and testing of WAF solutions. However, the sensitivity of these methods may limit their applicability.

In accordance with Annex VII, these short-term studies do not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur. For example, if the substance is highly insoluble in water (< 1 µg/l) or the substance is unlikely to cross biological membranes. In addition, the short-term study on invertebrates or fish does not need to be conducted if the corresponding (i.e. on invertebrates or fish, respectively) long term aquatic toxicity study is available.

9.1.4. The test is technically feasible also with NCSs of Botanical origin. It is not required if the substance is readily biodegradable (see § 9.2.1.1) and PEC<sup>7</sup>s are below or equivalent to the test concentrations applied, or if there are mitigating factors indicating that aquatic toxicity is unlikely to occur. For example, if the substance is highly insoluble in water (< 1 µg/l).

9.1.5/6. The present tests needs adaptation. Recommendations for testing mentioned in 9.1.1./2./3. (e.g. WAF methodology, sealed system to prevent volatility) also apply to these tests. A continuous flow of test solutions is recommended for long-term fish testing. The long-term study on fish is not necessary if PEC/PNEC<sup>8</sup> < 1 based on the *Daphnia* long-term result and an assessment factor of 50.

9.2.1.1. The present test is considered as not feasible for an NCS of botanical origin because the standard protocols have been established to state on ready biodegradability of mono-constituent substances. The ready biodegradability of all constituents of a complex mixture such as an NCS of botanical origin can not be demonstrated when testing the NCS using these current protocols.

A specific protocol needs to be developed for NCS being incompletely characterized and consisting of a large number of unidentified constituents (the majority of botanicals and botanical extracts to be registered under REACH). Unknown constituents, if possible, may be identified by a generic description of their chemical nature and, if possible, groups of related structures could be used for the assessment.

An assessment as to whether an NCS being completely characterized is likely to pass a ready test could be made using this specific test, or experimental data and/or valid (Q)SAR<sup>9</sup> / read-across predictions for the constituents.

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<sup>6</sup> OECD (2000): OECD Series on Testing and Assessment, Number 23, Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, 15 December 2000

<sup>7</sup> Predicted Environmental Concentrations

<sup>8</sup> Predicted No-Effect Environmental Concentrations

<sup>9</sup> (Quantitative) Structure-Activity Relationship

9.2.1.2./3./4. The existing test protocols have been developed for single molecules which are preferably radio-labelled for this purpose. Therefore these tests are considered as not feasible for an NCS of botanical origin.

Further biotic degradation testing is not required if the substances is readily biodegradable or is highly insoluble in water (< 1 µg/l). If the CSA indicates that degradation needs to be further investigated the evaluation with respect to persistency properties may proceed by reference to experimental data and/or valid (Q)SAR / read-across predictions for those constituents and/or representative structures of concern.

9.2.2.1. This test is not adapted to complex mixtures. It is not required if the substance is readily biodegradable or is highly insoluble in water (< 1 µg/l)

9.3.1. This test is not adapted to complex mixtures, because of analytical monitoring issues. In addition, the adsorption coefficient (Koc) of an NCS has little meaning. The OECD 121 using the HPLC technique is suitable to determine the adsorption coefficient of the individual constituents. Alternatively a range of Koc can be given from the calculated or measured values of constituents and/or representative structures.

9.3.2./3. The existing test protocols have been developed for single molecules which are preferably radio-labelled for this purpose. Therefore this is considered as not feasible for an NCS of botanical origin.

BCF testing is not needed if the substance has a low potential for bioaccumulation (for instance all constituents have log Kow < 3). If the CSA indicates that bioaccumulation needs to be further investigated the evaluation may proceed by reference to experimental data and/or valid (Q)SAR / read-across predictions for those constituents and/or representative structures which have been identified as of greatest concern. It is proposed that the B screening criteria from the PBT/vPvB assessment (e.g. log Kow > 4.5) will be used to identify those constituents or NCS substances that may have bioaccumulation potential. If a further confirmatory step is needed, the most highly bioaccumulative constituent(s) may be selected for bioaccumulation testing (assuming they can be extracted or synthesized).

9.3.3. The existing test protocols have been developed for single molecules which are preferably radio-labeled for this purpose. Therefore these are considered as not feasible for an NCS of botanical origin.

9.4.1./2./3./4./6. The tests are technically feasible also with NCSs of Botanical origin. The choice of the appropriate tests depends on the outcome of the CSA

These tests do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. In addition, the short-term study on earthworms or plants does not need to be conducted if the corresponding (i.e. on earthworms or plants, respectively) long term terrestrial toxicity study is available.

9.5.1. NCSs of Botanical origin being complex mixtures of components with variable physico-chemical properties (water solubility, volatility, stability, adsorption ...) create special difficulties with the present test protocols which will require adaptation (e.g. use of the WAF procedure to prepare test solutions, particular analytical investigations). Further details are given in 9.1.1./2./3

9.6.1. The test is technically feasible also with NCSs of Botanical origin.

## 5. Bibliography

Regulation (EC) N° 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) N° 793/93 and Commission Regulation (EC) N° 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EEC and 2000/21/EC, Official Journal of the European Union L 396, 30 December 2006.

Directive 67/548/EEC of the Council of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

The European Cosmetics Association (COLIPA), the International Association for Soaps, Detergents and Maintenance Products (AISE), the International Fragrance Association (IFRA), the European Flavour and Fragrance Association (EFFA), the European Federation of Essential Oils (EFEO), the International Federation of Essential Oil and Aroma Trade (IFEAT), the European Organization for Cosmetic Ingredients Industries and Services (UNITIS), the European Herb Growers Association (EUROPAM), L'Office National Interprofessionnel des Plantes à Parfum, Aromatiques et Médicinales (Onippam): The registration for REACH of Natural Complex Substances used as Fragrance Ingredients, 29 August 2007;

EFSA Guidance document of the Scientific Committee "Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements", 2007.

ECHA Guidance for identification and naming of substances under REACH, June 2007;  
[www.echa.europa.eu/](http://www.echa.europa.eu/)

ECHA Guidance on information requirements and Chemical Safety Report, May 2008;  
[www.echa.europa.eu/](http://www.echa.europa.eu/)

## 6. ANNEXES

### Annex 1:

Categories of Natural Complex Substances used in cosmetics, Natural Alliance, September 2008.

### Annex 2:

Separation of the botanical fraction from its carrier or carrying solvent, UNITIS, November 2008.

### Annex 3:

Draft Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, EFSA (European Food Safety Authority) 2007.

### Annex 4:

NCS of botanical origin: examples of NCS identification.

***This voluntary industry guidance for the registration under REACH of NCS used as cosmetic ingredients is a living document. New methods for their testing and assessment will be evaluated and, if validated, this guidance shall be updated accordingly.***



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## **NATURAL ALLIANCE**

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**Registration under REACH of Natural Complex Substances (NCS)  
used as cosmetic ingredients:**

### **ANNEX 1**

#### **CATEGORIES OF NATURAL COMPLEX SUBSTANCES USED IN COSMETICS**

Botanical Extracts and Derivatives  
Essential oils  
Botanical Lipids  
Animal Extracts and Derivatives  
Animal Lipids  
Micro-organisms/Biomass Extracts and Derivatives  
Mineral Substances and derivatives

# Listing by categories of EXTRACTS and DERIVATIVES from BOTANICALS of earth and aquatic and MUSHROOMS

PRODUCTS CATEGORIES	EXAMPLES
<p style="text-align: center;"><b>CATEGORY 1</b></p> <p><b>Plants, part of plants and plant products</b></p>	<ul style="list-style-type: none"> <li>* Apricot Kernel powder</li> <li>* Tiare Flower</li> <li>* Kiwi Seeds</li> <li>* Aloe Vera gel</li> <li>* Resins</li> <li>* Exsudates</li> <li>* Starch</li> </ul>
<p style="text-align: center;"><b>CATEGORY 2</b></p> <p><b>Liquid or Dry Aqueous extracts</b></p>	<ul style="list-style-type: none"> <li>* Aqueous liquid extract of Chamomile</li> <li>* Aqueous dry extract of Green tea</li> <li>* Floral water of Cornflower</li> <li>* Oat proteins</li> <li>* Rose Water</li> <li>* Orange flower water</li> </ul>
<p style="text-align: center;"><b>CATEGORY 3</b></p> <p><b>Essential Oils</b></p>	<ul style="list-style-type: none"> <li>* Lavender Oil</li> <li>* Citrus Oils</li> </ul>
<p style="text-align: center;"><b>CATEGORY 4</b></p> <p><b>Non aqueous Liquid extracts :</b></p> <ul style="list-style-type: none"> <li>▪ <b>Glycolic</b></li> <li>▪ <b>Ethanolic</b></li> <li>▪ <b>Glycerinated</b></li> <li>▪ <b>Oily</b></li> <li>▪ <b>All combinations of these solvents including water</b></li> </ul>	<ul style="list-style-type: none"> <li>* Hydroglycolic extract of Calendula</li> <li>* Glycerinated extract of Hibiscus</li> <li>* Oily macerate of Carrot</li> <li>* Sabal serrulata CO2 extract</li> </ul>
<p style="text-align: center;"><b>CATEGORY 5</b></p> <p><b>Non aqueous Dry extracts or Fractions :</b></p> <ul style="list-style-type: none"> <li>▪ <b>Concentrated and Titrated extracts</b></li> <li>▪ <b>Extracted Fractions</b></li> </ul>	<ul style="list-style-type: none"> <li>* Dry extract of ginseng 25% Ginsengosides</li> <li>* Centella asiatica sesquiterpenic fraction</li> <li>* Plant proteins, peptides and amino acids</li> <li>* Meristem</li> </ul>
<p style="text-align: center;"><b>CATEGORY 6</b></p> <p><b>Non aqueous Extracts or Fractions dried on a medium :</b></p> <ul style="list-style-type: none"> <li>▪ <b>Concentrated and Titrated extracts</b></li> <li>▪ <b>Extracted Fractions</b></li> </ul>	<ul style="list-style-type: none"> <li>* Spray dried extract on Dextrin, Lactose, Starch..</li> <li>* Lyophilized extract on Dextrin, Lactose, Starch..</li> </ul>

## Listing by categories of LIPIDS from BOTANICALS of earth and aquatic and MUSHROOMS

PRODUCTS CATEGORIES	EXAMPLES
<p style="text-align: center;"><b>CATEGORY 1</b></p> <p><b>Pressed Oils, Butters and Waxes:</b></p> <ul style="list-style-type: none"> <li>▪ <b>Virgin</b></li> <li>▪ <b>Deodorized</b></li> <li>▪ <b>Decolorized</b></li> <li>▪ <b>Degummed</b></li> <li>▪ <b>Refined</b></li> </ul>	<ul style="list-style-type: none"> <li>* Virgin Sweet Almond Oil</li> <li>* Refined Avocado Oil</li> <li>* Deodorized Kokum Oil</li> <li>* Shea Butter</li> <li>* Jojoba Oil</li> </ul>
<p style="text-align: center;"><b>CATEGORY 2</b></p> <p><b>Solvents extracted Oils, Butters and Waxes</b></p>	<ul style="list-style-type: none"> <li>* Borage Oil</li> <li>* Pomegranate Oil</li> <li>* Blackcurrant seeds Oil</li> <li>* Shea Butter solvent extracted</li> </ul>
<p style="text-align: center;"><b>CATEGORY 3</b></p> <p><b>Hydrogenated oils</b></p>	<ul style="list-style-type: none"> <li>* Perhydrosqualene</li> <li>* Hydrogenated Avocado Butter</li> </ul>
<p style="text-align: center;"><b>CATEGORY 4</b></p> <p><b>Lipid fractions :</b></p> <ul style="list-style-type: none"> <li>▪ <b>Unsaponifiable fractions</b></li> <li>▪ <b>Lecithins</b></li> <li>▪ <b>etc.</b></li> </ul>	<ul style="list-style-type: none"> <li>* Unsaponifiable of Olive Oil</li> <li>* Unsaponifiable of Shea</li> <li>* Phytosterols</li> <li>* Tocopherols</li> <li>* Glycerides</li> </ul>
<p style="text-align: center;"><b>CATEGORY 5</b></p> <p><b>Fatty acids, their salts and methylester</b></p>	<ul style="list-style-type: none"> <li>* Stearic acid</li> <li>* Arachidonic acid</li> <li>* Zinc stearate</li> </ul>

## Listing by categories of EXTRACTS and DERIVATIVES from ANIMAL origin

PRODUCTS CATEGORIES	EXAMPLES
<p style="text-align: center;"><b>CATEGORY 1</b></p> <p><b>Part of animals and animal products</b></p>	<ul style="list-style-type: none"> <li>* Silk</li> <li>* Oystershell-powder</li> <li>* Honey</li> <li>* Propolis</li> </ul>
<p style="text-align: center;"><b>CATEGORY 2</b></p> <p><b>Liquid or Dry Aqueous extracts</b></p>	<ul style="list-style-type: none"> <li>* Cochenille red</li> <li>* Roe extract</li> <li>* Thymus extract</li> <li>* Cell extract</li> <li>* Native collagen</li> <li>* Native elastin</li> </ul>
<p style="text-align: center;"><b>CATEGORY 3</b></p> <p><b>Non aqueous Liquid extracts :</b></p> <ul style="list-style-type: none"> <li>▪ Glycolic</li> <li>▪ Ethanolic</li> <li>▪ Glycerinated</li> <li>▪ Oily</li> <li>▪ All combinations of these solvents including water</li> </ul>	<ul style="list-style-type: none"> <li>* Oyster extract</li> </ul>
<p style="text-align: center;"><b>CATEGORY 4</b></p> <p><b>Non aqueous Dry extracts or Fractions :</b></p> <ul style="list-style-type: none"> <li>▪ Concentrated and Titrated extracts</li> <li>▪ Extracted Fractions</li> </ul>	<ul style="list-style-type: none"> <li>* Hydrolyzed elastin</li> <li>* Hydrolyzed collagen</li> <li>* Chitin</li> <li>* Hydrolyzed human hairs</li> <li>* DNA</li> </ul>
<p style="text-align: center;"><b>CATEGORY 5</b></p> <p><b>Non aqueous Extracts or Fractions dried on a medium.</b></p> <ul style="list-style-type: none"> <li>▪ Concentrated and Titrated extracts</li> <li>▪ Extracted Fractions</li> </ul>	<ul style="list-style-type: none"> <li>* Spray dried extract on Dextrin, Lactose</li> <li>* Lyophilized extract on Dextrin, Lactose</li> </ul>

## Listing by categories of LIPIDS from ANIMAL origin

PRODUCTS CATEGORIES	EXAMPLES
<b>CATEGORY 1</b> Part of animals and animal products	* Milk * Tallow * Butter
<b>CATEGORY 2</b> Lipidic Fractions	* Lanolin * Animal squalene * Astaxanthin ex shrimps

## Listing by categories of EXTRACTS and DERIVATIVES of MICRO-ORGANISMS/BIOMASS

PRODUCTS CATEGORIES	EXAMPLES
<p style="text-align: center;"><b>CATEGORY 1</b></p> <p><b>Micro-organisms/ Biomass</b></p>	<ul style="list-style-type: none"> <li>* Yeast</li> <li>* Sea fennel stem cells</li> </ul>
<p style="text-align: center;"><b>CATEGORY 2</b></p> <p><b>Substances obtained from micro-organisms and/or biomass</b></p>	<ul style="list-style-type: none"> <li>* Bifida ferment extract</li> <li>* Amino acids</li> <li>* Xanthan</li> <li>* Peptides</li> <li>* Quark</li> <li>* Proteins</li> <li>* Glycanes</li> <li>* Hyaluronic acid</li> </ul>
<p style="text-align: center;"><b>CATEGORY 3</b></p> <p><b>Dry or Liquid extracts or Fractions obtained from microorganisms and /or biomass :</b></p> <ul style="list-style-type: none"> <li>▪ <b>Concentrated and Titrated extracts</b></li> <li>▪ <b>Extracted Fractions</b></li> </ul>	<ul style="list-style-type: none"> <li>* TIMPs</li> <li>* Astaxanthin ex algae</li> <li>* Microalgae CO<sub>2</sub> extract</li> </ul>

## Listing by categories of SUBSTANCES and DERIVATIVES of MINERAL origin

PRODUCTS CATEGORIES	EXAMPLES
<p style="text-align: center;"><b>CATEGORY 1</b></p> <p><b>Minerals</b></p>	<ul style="list-style-type: none"> <li>* Talcum powder</li> <li>* Diamond powder</li> <li>* Gold chips</li> </ul>
<p style="text-align: center;"><b>CATEGORY 2</b></p> <p><b>Minerals in natural waters</b></p>	<ul style="list-style-type: none"> <li>* Dead sea water</li> <li>* Dead sea salt</li> <li>* Dried sea water</li> </ul>
<p style="text-align: center;"><b>CATEGORY 3</b></p> <p><b>Mineral soils and mixtures of them</b></p>	<ul style="list-style-type: none"> <li>* Mud</li> <li>* Peat</li> <li>* Bog</li> <li>* Silt</li> <li>* Numijo earth</li> </ul>
<p style="text-align: center;"><b>CATEGORY 4</b></p> <p><b>Extracts from minerals or mineral soils</b></p>	<ul style="list-style-type: none"> <li>* Peat extract</li> <li>* Silt extract</li> </ul>



## Registration under REACH of Natural Complex Substances (NCS) used as cosmetic ingredients

### Annex 2

#### NCS OF BOTANICAL ORIGIN:

#### SEPARATION of the BOTANICAL FRACTION from its CARRIER or CARRYING SOLVENT

##### 1. Preamble

Natural Complex Substances (NCS) of botanical origin used in cosmetics and other types of consumer products are very often delivered on the market in a carrier or a carrying solvent used for extraction and/or for facilitating its use.

In view of REACH Pre-registration and Registration, the definition of a substance provided in the REACH Regulation has to be taken in account:

*“A chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, **but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.**”*

The aim of this document is to review all possible techniques available to manufacturers of NCSs of botanical origin in order to separate such NCSs from their carrier or carrying solvent, in compliance with the definition of a substance. The purpose of these procedures is to identify the substances to be registered and to determine their tonnage band.

Within such a context, the separation of a NCS from its carrier or carrying solvent is also dedicated to isolate the NCS on which tests can be performed.

Where the solvent cannot be totally removed, it is up to the registrant to eliminate the solvent down to the adequate level.

Consequently:

- either the botanical fraction can be isolated during the process before mix with its carrier or carrying solvent,
- or the separation techniques used have to be adapted with the view to guarantee that it will not affect the stability of the botanical fraction or change its composition, as far as it can be determined with routine techniques.

## **2. Carriers or carrying solvents**

Carriers or carrying solvents used by manufacturers of NCS of botanical origin used in cosmetics and other types of consumer products are, for example, the following (or mixtures of these):

- Water (Acqua)
- Propylene glycol
- Butylene glycol
- Ethanol
- Glycerol
- Vegetable oils
- Fatty acids esters
- Maltodextrin/Lactose/Soluble Fibers

## **3. Separation techniques**

The general methods for measurement of dry residue recommended by Pharmacopoeia fix an evaporation temperature of 105°C that can significantly affect the NCS of botanical origin. It is consequently not adapted.

Separation of NCS of botanical origin from their carrier or carrying solvent can be obtained through adapted methods depending upon the carrier or the carrying solvent used, such as described below:

### **3.1. WATER**

Water can be removed mainly through the following evaporation techniques:

- Lyophilisation
- Evaporation under vacuum
- Spray drying
- Oven drying
- Halogen technique

The selection of the accurate method has to be made in accordance with the sensitivity of the botanical fraction, especially in terms of temperature.

### **3.2. PROPYLENE GLYCOL/BUTYLENE GLYCOL**

Propylene glycol and Butylene glycol can be removed mainly through the following adapted evaporation techniques:

- Evaporation under vacuum
- Oven drying at low temperature
- Halogen technique

The selection of the accurate method has to be made in accordance with the sensitivity of the botanical fraction, especially in terms of temperature. It is especially recommended not to exceed 80°C.

### **3.3. MIXTURES of WATER and PROPYLENE GLYCOL / BUTYLENE GLYCOL**

Whatever are their proportions, such mixes can be removed mainly through the following evaporation techniques valid for both water and propylene glycol/butylene glycol :

- Evaporation under vacuum

- Oven drying at controlled temperature
- Halogen technique

The selection of the adequate method has to be made in accordance with the sensitivity of the botanical fraction, especially in terms of temperature.

In this field, verification tests performed show that, for carrying solvents containing less than 70% of Glycol, it is especially recommended not to exceed 80°C.

#### 3.4. *ETHANOL*

Ethanol can be removed through same evaporation techniques and conditions as for WATER:

- Lyophilisation
- Evaporation under vacuum
- Spray drying
- Oven drying
- Halogen technique

The selection of the adequate method has to be made in accordance with the sensitivity of the botanical fraction, especially in terms of temperature.

#### 3.5. *GLYCEROL / MIXTURES of WATER-GLYCEROL*

The extraction of a botanical material with glycerol or a mixture of water and glycerol does not always result in a NCS that can be isolated. A read-across approach might need to be considered (e.g. performing the tests on an extract obtained with a volatile solvent of an equivalent polarity).

#### 3.6. *VEGETABLE OILS and FATTY ACID ESTERS*

The extraction of a botanical material with a vegetable oil or a fatty acid ester does not always result in a NCS that can be isolated. A read-across approach might need to be considered (e.g. performing the tests on an extract obtained with a volatile solvent of an equivalent polarity).

#### 3.7. *MALTODEXTRIN / LACTOSE / SOLUBLE FIBERS*

Maltodextrin, Lactose and Soluble fibers are carriers used as diluents and/or supports during spray drying NCS of Botanical origin in aqueous or aqueous/ethanolic solutions.

Consequently, the NCS can be isolated in the phases of process preceding spray drying either directly as a dry substance or through evaporation techniques adapted for water and/or ethanol.

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

## **Guidance document of the Scientific Committee**

**(Question No EFSA-Q-2005-233)**

### **SCIENTIFIC COMMITTEE MEMBERS**

Sue Barlow, Andrew Chesson, John Collins, Erik Dybing, Albert Flynn, Claudia Fruijtier-Pölloth, Tony Hardy, Ada Knaap, Harry Kuiper, Pierre Le Neindre, Jan Schans, Josef Schlatter, Vittorio Silano, Staffan Skerfving and Philippe Vannier.

### **SUMMARY**

Following the discussion paper of the Scientific Committee on botanicals and botanical preparations adopted on 23 June 2004 and the mandate received by the Scientific Committee in August 2005 from EFSA, the Scientific Committee developed a two-level approach for the safety assessment of botanicals and botanical preparations.

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 was 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 would be subject to a more extensive safety assessment with the methodology further developed in the present document.

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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).

The Scientific Committee developed criteria for prioritising botanicals for safety assessment and has started to compile 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 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.

A public consultation was organised beginning of 2008 to submit the approach proposed by EFSA to stakeholders and give them an opportunity to provide EFSA with additional information for the Compendium. The comments received during the public consultation have been reviewed by the working group of the Scientific Committee and used to update the present guidance document. A summary of the main comments received by EFSA and how they were taken into account by the Scientific Committee is published together with this document.

As a follow up, an EFSA Scientific Cooperation (ESCO) Working Group on Botanicals has been created to enlarge the information in the Compendium and test the proposed approach for the safety assessment of botanicals and botanical preparations with a selected number of cases. It is expected that, based on the experience gained with this ESCO activity, there will be a need for an update of the present guidance document.

**Key words:**

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

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## **BACKGROUND AS PROVIDED BY EFSA**

A discussion paper of 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>1</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 the 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>2</sup>). Simultaneously, a cover note (Document AF 01.10.2004 – 3<sup>3</sup>) inviting 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) was provided to develop a clearer picture of the extent 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.

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

The Scientific Committee has been requested in August 2005<sup>4</sup> by the European Food Safety Authority:

1. To analyse the information provided by the 25 European countries in response to the questionnaire distributed to the members of the Advisory Forum in October 2004
2. To prepare a guidance document on how to assess the safety of botanicals and botanical preparations to be used in the food and feed area.
3. To establish a list of main categories of botanicals and botanical preparations and to prioritise the products to be considered for a safety assessment.

<sup>1</sup> See [http://www.efsa.europa.eu/science/sc\\_committee/sc\\_documents/616\\_en.html](http://www.efsa.europa.eu/science/sc_committee/sc_documents/616_en.html)

<sup>2</sup> See [http://www.efsa.europa.eu/EFSA/DocumentSet/af10\\_doc3a\\_botanicals\\_en1.0.pdf](http://www.efsa.europa.eu/EFSA/DocumentSet/af10_doc3a_botanicals_en1.0.pdf)

<sup>3</sup> See [http://www.efsa.europa.eu/EFSA/DocumentSet/af10\\_doc3\\_botanicals\\_en1.0.pdf](http://www.efsa.europa.eu/EFSA/DocumentSet/af10_doc3_botanicals_en1.0.pdf)

<sup>4</sup> See [http://www.efsa.europa.eu/EFSA/Scientific\\_Document/sc\\_com\\_mandate\\_botanicals\\_approach1.0.pdf](http://www.efsa.europa.eu/EFSA/Scientific_Document/sc_com_mandate_botanicals_approach1.0.pdf)

In the preparation of its guidance document, the Scientific Committee is requested:

- To take into consideration the legislative framework and other legislative developments in this area.
- To take into account the activities conducted by the European Medicines Agency (EMA), in particular the Committee on herbal medicinal products (HMPC<sup>5</sup>).
- To consider the related activities already conducted by other relevant organisations, such as the French Food Safety Agency (AFSSA, 2003), the Council of Europe (Council of Europe, 2005), and ILSI Europe (Schilter *et al.*, 2003).
- To take into account the work carried out by the Scientific Panels.

#### **ACKNOWLEDGEMENTS**

The European Food Safety Authority wishes to thank the members of the Working Group for the preparation of this guidance document: Vittorio Silano (Chair), Robert Anton, Angelo Carere, Andrew Chesson, Luc Delmulle, Corrado Galli, Christophe Nguyen-The, Kirsten Pilegaard, Ivonne Rietjens and Gerrit Speijers.

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<sup>5</sup> See <http://www.emea.europa.eu/htms/general/contacts/HMPC/HMPC.html>

## ASSESSMENT

### 1. Introduction

A public consultation was organised beginning of 2008 to submit the approach proposed by EFSA to stakeholders and give them an opportunity to provide EFSA with additional information for the compendia. The comments received during the public consultation have been reviewed by the working group of the Scientific Committee and used to update the present guidance document. A summary of the main comments received by EFSA and how they were taken into account by the Scientific Committee is published together with this document.

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>6</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 conceptual framework for safety assessment was proposed by the Scientific Committee, in which botanicals or botanical preparations for which an adequate body of knowledge exists (as further described in the present guidance document regarding their safety of use under specific conditions) should 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. EFSA should use as an example the Qualified Presumption of Safety (QPS) approach developed for microorganisms in food and feed<sup>7</sup>, 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 with a methodology to be developed by EFSA.

In order to facilitate the implementation of the above-mentioned approach, EFSA will compile 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 periodically updated by EFSA making use of relevant national lists and any other relevant documents available, as well as updated assessments carried out on botanicals and botanical products by expert committees of EU Agencies such as EFSA and EMEA,

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<sup>6</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)

<sup>7</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1178667590178.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178667590178.htm)

international bodies such as WHO, Council of Europe, and European Pharmacopoeia, and other organisations. This Compendium does not have any legal status and should be seen as a tool for EFSA and other interested parties 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.

## **2. Analysis of the information provided by the European countries in response to the questionnaire distributed to the Advisory Forum in October 2004**

The analysis of the answers given by the European countries in response to the questionnaire provided to the EFSA Advisory Forum members is available in Appendix A.

## **3. 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. Moreover, Regulation 1829/2003/EC on genetically modified food and feed would apply to any GMO ingredients used in food supplements. Therefore, the present guidance document does not apply to botanicals or botanical preparations that have to be assessed in the framework of other EU regulations in the food area.

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<sup>8</sup>.

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>9</sup>.

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

<sup>8</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1178620775770.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620775770.htm)

<sup>9</sup> See <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997H0618:EN:HTML>

Committee on Food on submissions for safety evaluation of sources of nutrients or of other ingredients proposed for use in the manufacture of foods<sup>10</sup> 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>11</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”<sup>12</sup>

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 4).

To ensure safety of botanicals and botanical preparations used in food supplements, a minimal set of data needs to be available. These include specification and characterization of the botanical or botanical preparation, determination of the intended use and of the ensuing exposure, characterization and assessment of the potential hazard(s). This implies that a range of technical, toxicological and exposure data are needed for the safety assessment of botanicals and botanical preparations that do not benefit from a “presumption of safety” status (see introduction and section 3.2.1).

### **3.1. 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>13</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.

The data required in this section aims at identifying and assessing the possible hazards associated with botanicals and botanical preparations.

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 possible 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

<sup>10</sup> See [http://ec.europa.eu/food/fs/sc/scf/out100\\_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out100_en.pdf)

<sup>11</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>12</sup> See [http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1178623592448.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178623592448.htm)

<sup>13</sup> See e.g. Reg. 178/2002, Reg. 852/2004, Reg. 853/2004, Reg. 854/2004.

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 3.2.1).

### **3.1.1. Technical data**

#### **3.1.1.1. Identity and nature of the source material**

- Identity, i.e. scientific (Latin) name (botanical family, genus, species, variety with author's name, chemotype if applicable)
- Common names<sup>14</sup>
- Part used (e.g. root, leaf, seed...)
- Geographical origin (continent, country, region)
- Growth and harvesting conditions (wild or cultivated; cultivation practices, time of harvest in relation to both season and stage of the plant growth)
- In the case of cultivated plants, the origin of the seed or propagules.

#### **3.1.1.2. 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 materials 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).

#### **3.1.1.3. Chemical composition**

Data on the chemical composition of the botanical ingredient should be provided with emphasis on compounds of relevance for the safety assessment.

#### **3.1.1.4. 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

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<sup>14</sup> If a trivial or a common name is used extensively in the monograph, it should be firmly linked to the scientific name and part used.

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.

#### **3.1.1.5. 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

#### **3.1.1.6. Proposed uses and use levels**

Information should be provided on the intended uses and recommended intakes for each botanical ingredient.

#### **3.1.1.7. Information on existing assessments**

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

### **3.1.2. Exposure: extent and time**

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 time.
- 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.

<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

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<sup>17</sup>.

### 3.1.3. 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.

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.

## 3.2. Proposed general framework for assessing the safety of botanicals and botanical preparations used as ingredients in food supplements

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

<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 without prior knowledge of the endpoints of concern.

<sup>17</sup> See [http://www.efsa.europa.eu/en/science/sc\\_committee/sc\\_opinions/uncertainty\\_exp.html](http://www.efsa.europa.eu/en/science/sc_committee/sc_opinions/uncertainty_exp.html)

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>18</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).

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 those on novel foods and GMOs, consists of the two following levels:

- Level A: Safety presumed based on available knowledge.
- Level B: Further testing and/or data required.

### **3.2.1. Level A: Safety presumed based on available knowledge**

Depending on the botanical ingredient and its uses, there are circumstances under which no additional data are judged necessary, *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 3.1 is 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

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<sup>18</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.

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.

In cases where toxic substances are known to be present in a botanical ingredients (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), or the Threshold of Toxicological Concern (TTC) covering the botanical ingredient under examination and all the other dietary sources.

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<sup>19</sup> 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 will not be significantly increased, compared to the intake from other sources.

Where a matrix effect is advocated to support the safety of particular levels of compounds (e.g. that data from a pure compound may overestimate effects of the compound 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.

For botanicals and botanical preparations listed in the Compendium (see Section 4 & Appendix B) with a potential to contain toxic, addictive, psychotropic or other substances that may be of concern, presumption of safety can be applied only if there is convincing evidence of the absence of significant levels of these undesirable substances in the specific plant parts or preparations (either because initially absent in the source material, or excluded, or inactivated during processing).

For botanical ingredients 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 (Compendium), with the understanding of the limitation that such an approach does not generally allow the assessment of possible synergistic or antagonistic effects.

### **3.2.2. Level B: Further data required**

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.

<sup>19</sup> See [http://www.efsa.europa.eu/en/science/sc\\_committee/sc\\_opinions/1201.html](http://www.efsa.europa.eu/en/science/sc_committee/sc_opinions/1201.html)

Moreover the possible impact of compounds of concern listed in the Compendium should be assessed, as indicated in section 3.2.1.

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 2001)<sup>20</sup>. 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

A botanical or botanical preparation should be tested for genotoxicity with the following two *in vitro* tests:

- A test for induction of gene mutations either in bacteria (e.g. OECD 471) or in mammalian cells (e.g. OECD 476), the latter in case of antimicrobial activity of the botanical ingredient.

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<sup>20</sup> See [http://ec.europa.eu/food/fs/sc/scf/out98\\_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out98_en.pdf)

- A test for induction of micronuclei (e.g. OECD 487<sup>21</sup>) or chromosomal aberrations (e.g. OECD 473) in mammalian cells.

Guidance on solvents which can be used for preparing test samples from botanicals and botanical preparations is provided for each of the above-mentioned mutagenicity tests in the above-mentioned OECD guidelines.

There may be circumstances under which it may be justified to deviate from the above-mentioned core set, or even not undertaking any genotoxicity testing. No genotoxicity testing would be for example required in the case of a botanical ingredient known to contain genotoxic compounds, that has a long history of food use, and whose intake level would not be significant, compared to “normal” sources. In such cases a scientific justification should be provided and additional types of considerations or mechanistic studies may be needed. Available genotoxicity data on isolated constituents of a botanical preparation could be used, but would normally not be considered sufficient in the absence of other data

One or more positive *in vitro* tests normally require 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 the appropriate *in vivo* test is critical, due to different sensitivities, different endpoints, toxicokinetic considerations 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. The choice of test should be based on all the information available, taking into account the recommendations for the follow-up testing in the EC Test Guidance Document<sup>22</sup>.

- Subchronic toxicity testing

A 90-day study in the rat with the test substance administered via the diet is the minimum requirement to establish a no-effect level. Subchronic toxicity testing should be carried out independently of the results of the *in vitro* and *in vivo* genotoxicity testing. However, a botanical or botanical preparation showing a genotoxic potential in both *in vitro* and *in vivo* tests would not be recommended for food supplement use, independently of the results of the subchronic toxicity study.

- 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 or immunotoxicity).

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<sup>21</sup> Guidelines under finalisation process – not yet adopted

<sup>22</sup> See [http://ecb.jrc.it/documents/TECHNICAL\\_GUIDANCE\\_DOCUMENT/EDITION\\_2/](http://ecb.jrc.it/documents/TECHNICAL_GUIDANCE_DOCUMENT/EDITION_2/)

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

##### **4.1. Methodological aspects**

A Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances that may be of concern has been produced by the ad-hoc working group.

The Scientific Committee takes note of this Compendium as a useful part of the preliminary work undertaken by EFSA to provide information in order to harmonise the methodology across its panels for assessing the safety of botanicals and botanical preparations used in food. The main purpose of this Compendium is to draw attention to issues which would need to be taken into account when assessing the safety of botanical ingredients for possible food supplement use and to facilitate the establishment of priorities for safety assessment. The main reason to make it available together with the present guidance document is to allow interested parties and the stakeholders to comment on it or to provide additional contributions to the Scientific Committee Secretariat. 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 described below contains the following information:

- The botanical (binomial) denomination of the plant (species and variety);
- The synonyms;
- The relevant part(s) of the plant and reference to the source(s) of information considered. The source of information is identified with its code (1 or 2 + a letter – see section 4.2)
- The reason(s) for concern in relation to the use in food supplement or additional elements of information concerning the medicinal use when applicable.

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.

##### **4.2. Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances that may be of concern**

The Compendium (see Appendix B) lists in alphabetical order botanicals reported to contain toxic, addictive, psychotropic, or other substances that may be of concern, without any judgment on whether these are suitable or not suitable for use in food supplements in Europe. The information sources utilized in order to produce such a Compendium are as follows:

- - **1A** – CPMP List of Herbal Drugs with Serious Risks, dated 1992 (CPMP / EMEA, 1992);

- - **1B** - Plants considered in 2005 by the Italian Ministry of Health as not suitable for use in food supplement manufacturing ([www.ministerosalute.it/alimenti/dietetica/dietetica.jsp](http://www.ministerosalute.it/alimenti/dietetica/dietetica.jsp));
- - **1C** - Spanish Regulation (Ministerio de Sanidad y Consumo Orden SCO/ 190/2004) concerning plants for which public sale is forbidden or limited because of toxicity;
- - **1D** - Swedish list (September 2006) concerning plants which are considered as not suitable in foods;
- - **1E** - Dutch Regulation implementing the Law 19 January 2001 on Goods and identifying pyrrolizidine alkaloids containing plants (for which a maximum limit of 1 µg/kg or per litre is imposed) (E1) and plants not to be used in herboristic products (E2);
- - **1F** - Belgian Regulation (29/8/1997 and following acts) identifying plants non admitted in foods;
- - **1G** - Danish list concerning toxicological evaluation of plants in food supplements; The list contains plants considered as unacceptable, plants with a restriction on daily use (max. level), and plants that are evaluated at a daily dose (“Droge listen” (2000) and later update (September 2006)
- - **1H** - Plants assessed as flavourings by the Council of Europe in 2000 and 2004 belonging to Category 3 or 4 (restrictions recommended for use) (H1 and H2 respectively) or as Category 5 (restrictions recommended and further data required) (H3) or Category 6 (considered not appropriate for human consumption) (H4);
- - **1I** - List of Botanicals not admitted or restricted in food in Austria; (Codex Unterkommission Nahrungsergänzungsmittel)
- - **1J** - The departmental order of the Danish Ministry of Health no. 698 (31. August 1993) List of euphorians. (Latest updated 11. April 2007)
- - **1K** - French Pharmacopoeia (10<sup>th</sup> edition): List of medicinal plants not suitable for food use (showing more adverse effects than benefits)
- - **1L** - Active principles (constituents of toxicological concern) contained in natural sources of flavourings. Council of Europe, 2004.
- - **2A** - Plants assessed as medicinal products by WHO in 1999 (Vol. I), 2002 (Vol. 2) and 2005 (Vol. 3);
- - **2B** - Plants assessed as medicinal products by the EMEA/HMPC since its inception, and previously by the Working Party on Herbal Medicinal Products between 1998 and 2004;
- - **2C** - Plants assessed as medicinal products by ESCOP (2003);
- - **2D** - Plants identified in the Belgian Regulation (Arrêté Royal 29/8/1997 – annex list 3 and following acts) as requiring a notification before marketing as food supplements;
- - **2E** - Final Public Statement on the use of herbal medicinal products containing estragole, Committee on Herbal Medicinal Products, London 23 November 2005;

- - **2F** - Monographs being prepared by the EMEA/HMPC;
- - **2G** - List of botanicals in which active principles, presently used in therapy, have been identified (Morelli and Vincieri, 1989).
- - **2H** - Final Public Statement on the use of herbal medicinal products containing methyleugenol, Committee on Herbal Medicinal Products (HMPC), London 23 November 2005
- - **2I** - Final Public Statement on capsicum/capsaicin containing herbal medicinal products, Committee on Herbal Medicinal Products (HMPC), London 23 November 2005
- - **2L** - Final Public Statement on the risk associated with the use of herbal products containing aristolochia species, Committee on Herbal Medicinal Products (HMPC), London 23 November 2005
- - **2M** - Final Public Statement on the use of herbal medicinal products containing pulegone and menthofuran, Committee on Herbal Medicinal Products (HMPC), London 23 November 2005
- - **2N** - Final Public Statement on the use of herbal medicinal products containing asarone, Committee on Herbal Medicinal Products (HMPC), London 23 November 2005
- - **2O** - The EuroFIR-NETTOX Plant List by Pilegaard K, Eriksen FD, Soerensen M, and Gry J. (2007) (Revised version of the NETTOX list of Food Plants - Major European Food Plants and Edible Mushrooms by 1997). European Food Information Resource Consortium (EuroFIR). ISBN 0 907 667 570.
- - **2P** - French Pharmacopoeia (10<sup>th</sup> edition): List of medicinal plants allowed for food application.
- List of traditional herbal substances, preparations and combinations thereof (Directive 2001/83/EC art. 16f, 1).
- European Pharmacopoeia and National Pharmacopoeia.

Several aspects related to botanicals appearing in this Compendium should be carefully considered, as toxicity can be related only to specific parts of the plant or to specific preparations; moreover, several processing techniques are known to remove or destroy toxic compounds possibly present and levels of toxic substances present may vary from one variety to another, or from one cultivar to another.

#### **4.3. Priority setting for safety assessment**

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

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 substances that are genotoxic and carcinogenic.

- 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 anecdotal or on the basis of case reports of intoxication, epidemiological data or any toxicity data from live-stock 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 level.

## **CONCLUSIONS AND RECOMMENDATIONS**

A two-level approach for the safety assessment of botanicals ingredients intended for use in food supplements is proposed. It allows the recognition of presumption of safety without further testing, based on long term history of use with no reported adverse effect. For those botanical ingredients for which a presumption of safety cannot be established, it introduces a framework for assessing their safety, including the types of testing that would be most useful. Criteria for prioritising botanicals for safety assessment are also suggested.

The initiated work listing in a Compendium botanicals that are reported to contain toxic, addictive, psychotropic or other substances that may be of concern, is considered to facilitate the assessment and should be further developed.

The Scientific Committee identified as a follow up the need to test the proposed approach for the safety assessment of botanical ingredients with a selected number of cases including some containing toxic constituents, and to develop further the information contained in the Compendium. The Compendium should be then periodically updated by EFSA, making use of relevant available national lists of plants and of any other relevant documents available, as well as of updated assessments carried out on botanicals by qualified bodies.

For this purpose, and in accordance with the strategy paper for cooperation and networking between the EU Member States and EFSA<sup>23</sup>, the Scientific Committee and the Advisory Forum identified this activity on the safety assessment of botanicals and botanical preparations as a "front-runner" project, suitable for an increased cooperation with the European Member States and other

<sup>23</sup>

See [http://www.efsa.europa.eu/EFSA/Event\\_Meeting/3%20AF%20Strategy%20For%20Cooperation%20and%20networking%202006%20-%20FINAL.3.pdf](http://www.efsa.europa.eu/EFSA/Event_Meeting/3%20AF%20Strategy%20For%20Cooperation%20and%20networking%202006%20-%20FINAL.3.pdf)

EU agencies, such as the EMEA. The following mandate has been prepared for an EFSA Scientific Cooperation (ESCO) Working Group on botanicals, consisting of experts from the EFSA Scientific Committee and Panels, as well as experts identified by the EU Member States.

The ESCO working group will be requested to complete the following terms of reference in a one-year timeframe:

- to enlarge the information in the Compendium, in order to improve its value.
- to select botanicals for safety assessment and test the proposed approach for the safety assessment of botanicals and botanical preparations with a selected number of cases.
- to provide the EFSA Executive Director with the updated Compendium and a report summarising the outcome of the case studies as well as to advise on the adequacy of the proposed approach for the safety assessment of botanicals and botanical preparations for EFSA and the Member States' needs.

It is expected that, based on the experience gained with this ESCO activity, there will be a need for further update of the draft framework for the safety assessment of botanical ingredients.

## REFERENCES

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## APPENDICES

### APPENDIX A - ANALYSIS OF THE ANSWERS PROVIDED BY THE EUROPEAN COUNTRIES<sup>24</sup> IN RESPONSE TO THE QUESTIONNAIRE DISTRIBUTED TO THE ADVISORY FORUM IN OCTOBER 2004

- *Is the issue of concern in your country?*

The fact that botanicals and botanical preparations intended for human consumption in food supplements or functional foods are more and more widely marketed with a variety of claims is considered as of moderate to major concern by the member States.

- *Is the issue formally addressed?*

Five countries do not formally address this issue. For the others, it consists mainly in assessing the products or substances of concern, and in setting measures to protect the consumers. Only seven countries reported to have some monitoring activities and two have market control systems in place.

- *Is national data available on the main categories of botanicals and botanical preparations currently on the market?*

Despite the indicated interest of the countries in this issue, only limited data are available: (i) 20% of the countries have national data that can be shared with EFSA; (ii) 40% of the countries have some data but not centralized and therefore difficult to access; and (iii) the remaining 40% of the countries apparently have no data available at all.

- *Do you have any information on the exposure of consumers to the types of botanicals or botanical preparations referred to in the discussion paper?*

When looking at available data on exposure, the situation is more problematic with 88% of the countries having no data at all. Two countries have some non-centralised data that will be difficult to access, and only one country has some partial data on the exposure of consumers to botanicals or botanical preparations.

- *What should be priority activities for EFSA in this area?*

The needs expressed by the Member States are similar:

- A negative list of botanicals and botanical preparations that should not be used for food supplementation
- A positive list of botanicals and botanical preparations suitable for food use, with established quantities that can be used, and a description of the criteria for a product to fulfil to be inserted on this list.
- A guidance document providing the reader with the definitions of what is a physiological / pharmacological / toxicological effect, and clarifying the border between a food and a medicine. The objective is to get some consistency between the different European countries with the classification of botanicals and botanical preparations and therefore to have a common approach with the assessment of these products. The guidance document should list as well the necessary documentation required to demonstrate the safety of a botanical or botanical preparation.
- A series of monographs documenting botanical sources and their biological activities.

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<sup>24</sup> Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Slovakia, Slovenia, Switzerland, Spain, United Kingdom.

- 1 APPENDIX B - EXTRACT OF THE COMPENDIUM OF BOTANICALS THAT HAVE BEEN REPORTED TO CONTAIN TOXIC, ADDICTIVE, PSYCHOTROPIC OR OTHER  
 2 SUBSTANCES THAT MAY BE OF CONCERN.

**COMPENDIUM OF BOTANICALS THAT HAVE BEEN REPORTED TO CONTAIN TOXIC, ADDICTIVE, PSYCHOTROPIC OR OTHER SUBSTANCES THAT MAY BE OF CONCERN**

*This Compendium lists in alphabetical order botanicals without any judgment on whether these are safe or not safe for food / feed applications in Europe. This Compendium is part of a preliminary work undertaken by EFSA to harmonise the methodology across its panels for assessing the safety of botanicals and botanical preparations used in food and feed. 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. This Compendium is still under development and open for additional contributions and comments.*

<b>Botanical name</b>	<b>Synonyms</b>	<b>Documented sources and parts of plants subject to restrictions</b>	<b>Items of information discussed in the source documents or provided by WG Experts</b>
<b><i>Abrus precatorius L.</i></b>		1B <sup>25</sup> : seeds 1C: entire plant 1F: unspecified parts	protein abrin and glycoside of abric acid
<b><i>Achyrocline satureioides DC</i></b>		1F: unspecified parts	devoid of acute toxicity but no medicinal use
<b><i>Acokanthera ouabaio cath.</i></b>		1B: wood, seeds	cardiotonic glycosides used only as intravenous poison (arrow); g-Strophanthin (Ouabain)
<b><i>Acokanthera schimperi Benth. Et Hook</i></b>		1B: fruit, wood	cardiotonic glycosides used only as intravenous poison (arrow); g-Strophanthin (ouabain)

3

<sup>25</sup> For explanation of abbreviations, see Compendium



## Registration under REACH of Natural Complex Substances (NCS) used as cosmetic ingredients

### Annex 4

#### NCS OF BOTANICAL ORIGIN

#### EXAMPLES OF NCS IDENTIFICATION

##### EXAMPLE 1: Identification of BAGURA SOFT BUTTER

- **Substance designation**

- Trade name and/or Internal Code / Reference:

BAGURA SOFT BUTTER

- Common name:

Hydrogenated Calophyllum Inophyllum Oil

- EINECS number:

269-820-6

- CAS number:

68334-28-1

- **Botanical Identity**

- Scientific name:

Calophyllum Inophyllum L. Clusiaceae

- Part of plant used:

NUT KERNEL

- **Origin and Traceability**

- Geographical origin of the plant:

VANUATU

- Location of growth and harvesting :

- Very clean and protected islands seashores in non polluted areas
- Natural growth on the coral reefs.

- Growth and harvesting conditions:

- . Wild or cultivated:

Wild picking by local harvesters trained on the botanical identification of the trees.

- . Time of collection or harvesting in relation to both season and stage of the plant growth:  
JULY

- . Collection or harvesting practices:

Fully manual picking

- . Pre- and post-harvest phyto-sanitary treatments, including use of pesticides:

No phyto-sanitary treatment either during growth or after harvesting.

- Description of primary processing:

- Sun drying during 60 days on openwork wooden riddles
- Mechanical cold pressing of Nut kernels to obtain a virgin oil

- Storage conditions:

The oil is stored in closed 1000 litres food grade polyethylene containers.

- Transport conditions:

Boat to the airport and airfreight to Europe in closed 1000 litres food grade polyethylene containers.

- Control and identification at reception with adapted methods:

Control through batch Number upon departure and arrival.

- **Process**

- Solvent(s) used:

None

- Characteristic steps of the extraction process:

- Cold pressing of nut kernels
- Partial hydrogenation with food grade catalyst
- Elimination of catalyst by filtration
- Water washing
- Drying
- Filtration
- Addition of 0.2% natural tocopherol as an antioxidant
- Cooling

- In-process and final controls:

- In-process:

Temperature and homogeneity

- Final:

- Control of full specifications at the end of the process
- New control after packaging on representative samples

- **Specifications**

- Physical and chemical parameters:

Appearance at 20°C	Soft solid
Colour	Pale green grey
Odour	Typical
Melting point °C	52 - 62
Solidification point °C	40 - 50
Acid value	AGL (FFA) 20 Max.
Saponification index	175 - 200
Iodine index (Wijs)	55 - 80

- Analytical controls through adapted methods:

- o *Main significant components:*

**\* TRIGLYCERIDES :**

<b>Fatty acids profile</b>	<b>%</b>
Palmitic [C16:0]	14,8
Stearic [C18:0]	38,7
Oleic [C18:1]	28,3
Linoleic [C18:2]	16,9
Linolenic [C18 :3]	0.1
Arachidic[C20 :0]	0,6
Gadoleic [C 20.1]	0,1
Behenic [C22 :0]	0,2

**\* STEROLS :**

$\beta$ -Sitosterol, Stigmasterol and Campesterol

- Identified toxicologically significant components, if potentially present at a level of concern

Hemavathy & Prabhakar mention that the dried seed of Calophyllum Inophyllum contains 60,1% of lipids, among which 1,4% is composed of phospholipids.

The major components of these phospholipids are 2-aminoethylphosphatidates that include Phosphatidylethanolamine.

Through endogen phospholipases, these components can go through partial enzymatic hydrolysis and produce ethanolamine or 2-aminoethanol, substance listed as toxic and corrosive in the European Directive L216/34.

So as to verify this hypothesis, BAGURA SOFT BUTTER has been submitted to a detection test of ethanolamine by RMN spectroscopy.

**The results of this study show that ethanolamine is not detected on the proton and carbon-13 spectrum obtained from the analysis of the aqueous phase of BAGURA SOFT BUTTER.**

➤ Study in annex

- Possible contaminants:

NONE

- Stability data:

12 MONTHS

## **EXAMPLE 2: Identification of PURPLE CONEFLOWER EXTRACT**

- **Substance designation**

- Trade name and/or Internal Code / Reference:

PURPLE CONEFLOWER PHYTAMI

- Common name:

Purple Coneflower extract

- EINECS number:

289-808-4

- CAS number:

90028-20-9

- **Botanical Identity**

- Scientific name:

*Echinacea purpurea* (L.) Moench, Asteraceae

- Part of plant used:

ROOT

- **Origin and Traceability**

- Geographical origin of the plant:

FRANCE

- Location of growth and harvesting :

Beauce region

- Growth and harvesting conditions:

- . Wild or cultivated:

Cultivated

- . Time of collection or harvesting in relation to both season and stage of the plant growth:

September at the end of flowering

- . Collection or harvesting practices:

Mechanical harvesting  
according Good Agricultural and Collection Practices – GACP – Supplier’s commitment

. Pre-harvest phyto-sanitary treatments:

Fertilizers, chemical and manual weeding

- Description of primary processing:

- . Drying under hot air
- . Crushing at 500µm

- Storage conditions:

Bulk packed in woven polypropylene big bags

- Transport conditions:

Road

- Control and identification at reception with adapted methods:

- . Aspect
- . Macro and microscopic control
- . Loss on drying
- . Ash
- . CLHP dosage
- . TLC characterization according to European Pharmacopoeia
- . Microbiological analysis
- . Possible contaminants: pesticides, heavy metals

- **Process**

- Solvent(s) used:

Water/Ethanol blend

- Characteristic steps of the extraction process:

- Maceration
- Filtration
- Concentration under vacuum
- Drying by zeodration

- In-process and final controls:

➤ In-process:

- . Water content
- . Total ash
- . CLHP dosage
- . Microbiological control

➤ Final:

According to full specifications

- **Specifications**

- Physical and chemical parameters:

Parameters	Results
<b>Organoleptic analysis</b>	
Aspect	Limpid to opalescent liquid
Colour	Orange to orangey brown
<b>Physical and chemical characteristics</b>	
Density at 20°C	1.250 – 1.290
Refractive Index at 20°C	1.460 – 1.4840
Water content	≤ 5.0%
Glycerin content	≥ 95 %
Solubility in water	Soluble to slightly soluble
<b>Identification</b>	
CHLP dosage Caftaric and chicoric acids	≥ 0.5mg/g
<b>Microbiological control</b>	
Aerobic bacteria	10 <sup>5</sup> cfu/g
Yeast, moulds	Absence/g

- Analytical controls through adapted methods:

- *Main significant components:*

- Carbohydrates: polysaccharides, mainly of the glucorono-arabinoxylan (PSI) and arabino-rhamno-galactan (PSII) type
- Protids :glycoproteins
- Phenolic compounds:
  - 0.6 – 2.1% chicoric acid and derivatives
  - caffeic, chlorogenic, dicaffeoylquinic acids
- Alkylamides (0.01 – 0.04%)
- Essential oil (0.1 – 0.2%)

- Identified toxicologically significant components, if potentially present at a level of concern:

NONE

- Possible contaminants:

NONE

- Stability data:

24 MONTHS