Workshop on safety assessment of botanicals and botanical preparations

Report of the meeting on 24 November 2009 (9:00-16:30)
Royal Olympic Hotel, Athens (Greece)

Participants

The list of participants is annexed to this report.

1. Welcome and opening

Prof. Vittorio Silano welcomed the participants to the workshop. The purpose of this event was to present the outcome of the work from the EFSA Scientific Committee on the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, and discuss with European Member States' Competent Authorities, Representatives from the industry, the European Commission and the European Medicines Agency (EMEA) possible ways forward regarding the safety assessment of plant based food supplements in Europe.

Summarising the history of this EFSA activity on botanicals, Prof. Silano stressed the broad request received from the Member States' Representatives in the EFSA advisory Forum for some tools to assess the safety of botanical products. As a reply to this need, the EFSA Scientific Committee published in September 2009 a "toolkit" for safety assessment, composed of:

- A compendium of botanicals reported to contain toxic, addictive, psychotropic and other substances of concern[1]
- A guidance document for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements[2]
- An EFSA Scientific Cooperation (ESCO) report illustrating with six examples how to apply the proposed method for safety assessment described in the guidance document[1].

This toolkit was made available for the use of any person interested in assessing the safety of a botanical product; one objective of this workshop was therefore to get a common understanding among the participants on how to use this tool. It was underlined by Prof. Silano that the guidance document is not intended to transfer the responsibility of ensuring the safety of botanical food supplements to EFSA, this responsibility belonging to the manufacturers, but should rather be considered as a help on how to develop further the rationale about the safety of botanical products.

[1] See http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902876819.htm
[2] See http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902880131.htm

2. Guidance of the Scientific Committee for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements[2]

Mr. Bernard Bottex presented the guidance document developed by the EFSA Scientific Committee. The Scientific Committee focussed its work on botanical food supplements; the proposed approach for safety assessment is however applicable to other uses of botanicals and botanical preparations in the food and feed areas.

The guidance comprises three parts:

- A list of technical, exposure and toxicological data that will be needed to assess the safety of botanical ingredients.

- A two-steps approach for safety assessment.

A first level (level A) is making use of the information on history of food use in Europe and the above-mentioned data directly available from the literature. Provided that no significant increase of intake compared to historical levels of the botanical ingredient under consideration is expected due to the intended level of use in food supplements and 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, then a presumption of safety may be applied to the considered preparation without any further request for testing, as long as any substance of concern (see the Compendium) is either absent or below acceptable health-based guidance values in the final preparation. Question was raised about the possible application of the Qualified Presumption of Safety (QPS) approach, initially developed for microorganisms added to food, to botanicals. It was explained that the variability in chemical composition between botanical species or even subspecies, or between different parts of a same plant makes the direct transcription of the QPS approach to botanicals impossible. The possibility of adapting this approach, e.g. by adding some specific qualifications could be considered by EFSA as a possible future activity. It was clarified during the workshop that exposure to the substance(s) of concern can also be considered in relation to the Threshold of Toxicological Concern (TTC) values. The EFSA Scientific Committee and other organisations, such as ILSI Europe are currently or have been exploring the possibility of using the TTC approach for human health risk assessments.

In cases where the anticipated intake of the botanical ingredient is significantly higher than the estimated intake level, or where no historical intake level could be identified, then additional exposure data will have to be provided and assessed under the second level (level B) of the assessment. Where it was not possible to conclude on presumption of safety at the level A assessment because of lack of data on some toxicological aspects, then additional toxicological studies should be carried out and assessed under level B as well. The EFSA document provides some guidance on the type of studies needed in relation to the different toxicological endpoints.

For compounds that are genotoxic and carcinogenic, the guidance document recommends the Margin of Exposure (MOE) approach. The outcome of such an approach provides an indication on the level of priority regarding risk assessment but does not quantify the risk as such. Clarification was requested on what to do in case of a low MOE. Dr. Gerrit Speijers explained that in such case, the traditional “As Low As Reasonably Achievable” (ALARA) or a case by case approach can be used, e.g. when a matrix effect is advocated, on the basis of adequate data.

- A number of criteria for prioritising botanicals for safety assessment.

These criteria should be considered together with the compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances of concern, in order to identify botanicals of higher toxicological concern, as compared to those who have a long history of use and a low toxic potential.

3. Compendium of botanicals reported to contain toxic, addictive, psychotropic or other substances of concern[1].

Prof. Robert Anton presented the compendium on behalf of Dr. Luc Delmulle, Chair of the related ESCO working group, and who could not participate in the workshop.

The compendium comprises around 900 botanical entries, identifying for each of them the binomial name, the most common synonyms, the plant part containing compound(s) of concern, the chemical(s) of concern, specific remarks and references of relevance for a safety assessment.

The purpose of the compendium is to flag botanicals that contain some compounds of possible toxicological concern. It does not take into account any treatment allowing the elimination or control of the compounds of concern when making the preparation, nor does it bring any judgement whether the listed botanicals are safe or unsafe for food applications. In that sense, the compendium cannot be considered as a negative list, nor is it meant for regulatory purposes.

The compendium will help the risk assessor, once the botanical(s) present in the considered preparation have been identified, to identify the compound(s) of concern on which to focus the safety assessment, making then use of the guidance document to control that the considered preparation is harmless.

The compendium is a living document and is not intended to be a complete list of botanicals containing compounds of concern. The fact that a botanical is not present in the compendium can be due to the following reasons:

- No toxicological concern could be identified for this botanical
- This botanical was not considered in the various sources of information used by the Scientific Committee at the time the compendium was built up. A number of additional lists that could be considered to expand further the information contained in the compendium were mentioned during the workshop.

A number of botanicals that were listed in the sources of information, but for which not data, e.g. on the compound of concern could be found were moved to an “information lacking” list. These botanicals should be subject to further data search in order to decide whether they should be included or left out of the EFSA compendium.

The workshop’s participants highlighted the need for clarifying what is meant by “substances of concern” as well as the criteria considered for putting a plant in the compendium to be further clarified. It was also suggested to identify, when relevant, other sources for possible exposure to a given compound, and to indicate when specific populations are at risk

A number of participants underlined the fact that the current compendium is a mix of highly toxic herbs and botanicals of common use for which a proper HACCP system and adequate measures when making the preparation could allow for controlling the risks. EFSA made the choice to keep the compendium as a single list to allow a quick searchable overview of the botanicals and their compounds of concern. A single list makes also the compendium particularly useful in the case of plant mixtures, allowing a quick verification on eventual amounts of specific compounds common to several botanicals and that should therefore be added. It was moreover underlined that splitting the compendium between highly toxic plants and less toxic ones would have implied a safety assessment of the botanicals in the compendium and the building of positive / negative lists, which is outside the mandate of the EFSA Scientific Committee.

4. Case reports used to test the science-based approach for safety assessment[1]

The six examples selected by the ESCO working group to test the approach for the safety assessment of botanicals and botanical preparations described in the guidance document were presented by their Rapporteurs. The examples and rationale for selecting them are summarised in the table below:

Botanical	Preparation	Possible safety issue
Citrus aurantium L. ssp. *aurantium* L.	Hydroalcoholic extract of dried peel	Misidentification / adulteration
Camellia sinensis (L.) O. Kuntze	Dried green tea extract	Liver toxicity
Ocimum tenuiflorum L.	Dry leaves extract	Reproduction toxicity
Foeniculum vulgare Mill. ssp. *vulgare* var. *vulgare*	Dried fruits (water extract)	Genotoxic carcinogen
Linum usitatissimum L.	Dried ripe seeds	Phytoestrogens
Triticum aestivum L.	Wheat Bran	Low concern – presumption of safety

For testing purposes, each example was focused on one botanical, one part of plant, one type of preparation and a limited number of compounds of concern; the case study reports cannot therefore be considered as a formal safety assessment of the botanical preparations evaluated. However, a proper safety assessment would for example require the overall exposure (added exposure in the case of a compound present in several botanicals and whose intake could come from food, food supplements and medicinal products) to be considered.

A question was raised, when discussing the report on green tea, on the value of data obtained from clinical studies for the safety assessment. It was clarified that any type of data can be considered for the level A or B safety assessment, provided that it is relevant for the preparation considered. In the particular case of green tea, Dr. Birgit Dusemund explained that a number of clinical studies are currently being performed with isolated EGCG but are not completed yet and therefore, their results could not be considered at the time the working group was looking at this example.

5. Plant food supplements: levels of intake, benefit and risk assessment (PlantLIBRA)

Dr. Patrizia Restani presented the EU DG Research-funded project PlantLIBRA. This collaborative project under the seventh framework programme regroups 24 partners from 10 European and 4 non European countries, and is expected to start in early 2010. The project aims at building up a meta-database of composition, biologically active compounds, safety information, residues and contaminants linked to plant based food supplements. The project will make use of the EFSA compendium as a source of information for the meta-database. A number of work packages will also, among other, aim at:

- Characterizing main plant food supplements in the European market;
- Estimating the general intake of plant food supplements in Europe;
- Collecting data on adverse effects associated to plant food supplements and on possible substances of concern and developing further risk assessment of plant food supplements, using the EFSA guidance document as a starting point;
- Developing a methodology for benefit assessment of plant food supplement;
- Developing science-based models to assess the combination of risks and benefits from the consumption of plant-based food supplements.

Member States' competent authorities, EFSA, DG Health and Consumers and the stakeholders will be offered the possibility to advise on possible common work strategies and to follow the progress of the project on a regular basis.

The participants welcomed the announcement of this project that should provide additional experience in the area of botanical assessment.

6. Recommendations and possible ways forward

The EFSA Scientific Committee and Advisory Forum recommend all persons from the industry and Member States' Competent Authorities, responsible for the safety of botanical food supplements, to use the guidance document and the compendium developed by EFSA. Dr. Manfred Lützow from FEFANA announced that EFSA's work will already be considered for the re-evaluation of around 650 plants used by the feed industry.

The second recommendation of the Advisory Forum is for the Scientific Committee to expand the information contained in the compendium, making use of national lists that were not considered so far and incorporating data on botanicals that do not have a history of use in Europe. The participants confirmed the importance of developing further the information

contained in the Compendium and keeping it regularly updated with the latest sources of information made available; clarification should be provided on the definition of "substances of concern" and the criteria that were used to decide to insert a botanical in the compendium. EFSA is also recommended to incorporate information on botanicals that have no history of use in the European Union but that have a history of traditional use in third countries.

It was acknowledged during the workshop that, even if further improvement is always possible, the toolkit developed by EFSA is finalised enough to be used for full safety assessment of botanical preparations. Both commitment to test the proposed approach and interaction with EFSA to report back on possible limitations of the guidance document are therefore needed.

EFSA confirmed its appreciation for any feedback based on experience on how to improve the guidance document. In the same way, any additional data to be considered for compendium will be most appreciated. Any contribution to the EFSA guidance or the compendium to be considered by the EFSA Scientific Committee should be sent to Mr. Bernard Bottex (Bernard.bottex@efsa.europa.eu).

Now that the EFSA toolkit is publicly available, the need for a platform where to benefit from the experience from the stakeholders, Member States competent authorities and European bodies regarding safety assessment of botanicals was expressed. EFSA will consider the possibility to organise on a yearly basis this type of workshop in order to discuss latest developments in this area and to provide some insights on how to best make use of the safety guidance documents. In relations to such tasks, the possibility of collaboration with the PlantLIBRA Project should also be considered in view of the large number and high representativity of the participating partners.

The relevance of such a platform was underlined for the assessment of botanical preparations, since it would require the involvement of EFSA, EU Member States, industry experts, and possibly of EMEA experts in the case of botanicals that are used both as medicinal products and food supplements.

Prof. Vittorio Silano and Dr. Djien Liem closed the meeting, thanking the participants for this open discussion on the science needed to assess the safety of botanicals and botanical preparations. They highlighted the importance of such interaction to reach some common understanding in Europe on how to perform safety assessment of botanicals. In that sense, EFSA remains open to any contribution to improve its toolkit.

List of Participants

- EFSA Experts:

Judith	**Amberg-Müller**	ESCO
Robert	**Anton**	ESCO
Birgit	**Dusemund**	ESCO
Andrea	**Lugasi**	ESCO
Kirsten	**Pilegaard**	ESCO
Mauro	**Serafini**	ESCO
Vittorio	**Silano**	Scientific Committee
Gerrit J. A.	**Speijers**	CONTAM Panel
Jaroslav	**Toth**	ESCO

- PlantLIBRA Coordinators:

Patrizia	**Restani**
Luca	**Bucchini**

- European Commission

Jeannie	**Vergnettes**	DG Health and Consumers - Unit 03

- EMEA

Olavi	**Pelkonen**	EMEA HMPC

- Stakeholders

Luca	**Battistini**	AESGP
Vaclav	**Bazata**	EHPM
Monika	**Beutgen**	EHIA
Patrick	**Coppens**	ERNA
Manfred	**Lützow**	FEFANA
Hartwig	**Sievers**	EBF
Marinella	**Trovato**	SISTE
Nico	**Van Belzen**	ILSI
Andreas	**Varlamos**	EFSA Stakeholder Platform

- EFSA Secretariat

Gian Luca	**Bonduri**	SCAF
Bernard	**Bottex**	SCAF
Lucilla	**Gregoretti**	FEEDAP
Georgi	**Grigorov**	SCAF
Leng	**Heng**	NDA
Djien	**Liem**	SCAF
Elena	**Marani**	SCAF
Torben	**Nilsson**	SCAF

- Member States' Competent Authority Representatives:

Ilze	**Abolina**	Latvia
Valérie	**Baduel**	France
Ulla	**Beckman-Sundh**	Sweden
Zuzana	**Bírošová**	Slovakia
Ingrid	**Busuttil**	Malta
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Mette	**Christiansen**	Denmark
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Joris	**Geelen**	Belgium
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Barbara	**Jaworska-Łuczak**	Poland
Pia	**Knuthsen**	Denmark
Katarína	**Kromerová**	Slovakia
Hendrik	**Kuusk**	Estonia
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Maria Teresa	**Mendes Nogueira**	Portugal
Eleni	**Mitropoulou**	Greece
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Gatis	**Ozoliņš**	Latvia
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Maria Da Graça	**Ribeiro Campos**	Portugal
Florian	**Riedel**	Germany
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Snieguolė	**Šćeponavicienė**	Lithuania
Ursula	**Siim**	Estonia
Minna-Maija	**Väänänen**	Finland
Iliyna Dimova	**Yaneva-Balabanska**	Bulgaria
Flavia	**Zammit**	Malta
Magdalini	**Zika**	Greece