

**DFG - Senate Commission on
Food Safety**

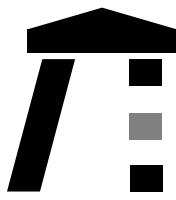
SKLM

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**Evaluation of food supplements containing other
ingredients than vitamins and minerals**

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The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG) has elaborated recommendations for the scientific assessment of the safety and nutritional benefit of food supplements with ingredients other than vitamins and minerals, in particular "other substances with nutritional or physiological effects". According to food law regulations, food supplements do not require an authorization before being placed on the market. The respective producer or distributor of food supplements has to ensure that the product is not harmful and that it is in accordance with the relevant legislation, particularly with the Directive 2002/46/EC, which was implemented into German law with the Regulation on Food Supplements (Verordnung über Nahrungsergänzungsmittel, NemV). However, in contrast to vitamins, minerals and trace elements, the use of "other substances with a nutritional or physiological effect" is not regulated by this directive. There is still a lack of scientifically substantiated criteria that are needed to assess the harmlessness, safety and health benefits of such "other substances". Nevertheless, there is an increasing use of such substances in foods and particularly in food supplements. The German opinion was adopted on 26th September 2006, the English version was accepted on 30th April 2007.

1 Goals

Food supplements are defined as food¹ intended to supplement the normal diet and which are concentrated source of nutrients or "other substances with a nutritional or physiological effect". They are marketed in dose form, such as capsules, tablets, etc. These "other substances" may be single substances or mixtures that have been obtained from animals, plants and microorganisms or which have been chemically synthesised.

Because these substances are consumed in a concentrated or isolated form, it is mandatory for preventative consumer health protection that they do not have adverse health effects when consumed in the intended quantities.

The SKLM considers a comprehensive safety assessment and scientific substantiation of the postulated nutritional or physiological effects of such food supplements to be essential within the interest of consumer health protection. This opinion addresses these topics and provides respective recommendations.

¹ This statement does not address legal classifications. Definitions of the used terms are given in the Glossary (Annex I). In this Opinion, the term "food supplements" is used for food supplements that contain exclusively or additionally "other substances with a nutritional or physiological effect". The term "food supplements" is equivalent to "dietary supplements".

2 Basic problems

It is not clear how "other substances with a nutritional or physiological effect" are to supplement the diet and whether undesirable effects can be reliably excluded. Due to the fact that these substances are usually no nutrients, there are no established recommendations with respect to recommended or maximum daily allowances. Some of the recommended dosages appear to be arbitrary or are based on experience from traditional use ("history of use"²) of these substances as a constituent of medicinal plants or foods. However, such experience from traditional use of these constituents cannot directly be applied to its use in a concentrated or isolated form.

From the scientific point of view, there is an urgent need to characterise food supplements, particularly those obtained as complex extracts from plant or animal materials, with respect to the raw materials, the manufacturing processes, and the relevant constituents. However, there are practically no science based standards in terms of identity and purity specification, as well as the characterisation of possible contaminants or accompanying substances.

Furthermore, the effects and mechanisms of action of "other substances" used in food supplements are often not studied adequately. Mechanistic information is usually limited to *in vitro* findings that cannot directly be applied to humans. Moreover, there is very little reliable data on intake of relevant constituents and their bioavailability from the food supplement.

In some cases, even substances that have previously been used in drugs are utilized in food supplements. As their efficacy and/or safety could not be scientifically proven, these drugs have either been withdrawn from the market or did not receive re-registration. Moreover, substances with a therapeutic purpose are also utilized that have not yet received authorisation as a drug. Occasionally substances with a pharmacological effect are utilized at dosages below those that are approved for therapeutic use. However, it is not at all proven that such a dosage is harmless.

² Categories of scientific evidence – human information and data, in [¹]

Food supplements are not intended for therapy of diseases and they must be safe also for long-term consumption. In contrast to drugs, food supplements are consumed without medical advice or monitoring of its tolerance by a physician. Moreover, it is not required to have a package information leaflet giving details of possible adverse effects. This may lead to a situation where consumers take the food supplement in a kind of self-medication or, because of ignorance or as a result of inappropriate information, even instead of or in addition to their medication. Adverse health effects cannot be excluded, e.g. when the recommended daily intake is exceeded or when interactions occur with drugs that are taken concomitantly. Moreover, multiple exposures caused by concomitant intake of several food supplements cannot be excluded either.

The Senate Commission is concerned that certain distribution channels considerably impede the monitoring of food supplement marketing. This particularly applies to preparations marketed via the internet and which may not be approved for retailing as food supplement in Germany.

3 Safety evaluation

To ascertain that the product is safe for the consumer, comprehensive tests and evaluations in agreement with the generally accepted principles of risk analysis (see Annex II) have to be performed.

Owing to the great diversity of the substances used in food supplements, a case-by-case study is generally required. Nature and extent of the necessary data concerning the food supplement or its physiologically, toxicologically and pharmacologically relevant constituents depend on previous information with respect to its traditional medicinal or food use, on the expected exposure of the target respective potential risk groups as well as on its mode of action.

The SKLM recommends that the basic toxicological data set required for safety evaluation of the food supplement should be collected/generated in compliance with internationally recognised guidelines for additives or for nutrients and other substances [^{2, 3}]. The application of the guideline for additives has already been recommended for functional foods in another opinion issued by the SKLM [⁴]. Individual cases may require additional studies that are also described in this guideline.

The assessment of a food supplement includes an individual evaluation of each relevant constituent. In addition, the assessment has to take into account the overall effect of the constituents in the food supplement or in the preparation (if applicable) because there may be mutual interactions affecting kinetics and mode of action of the individual substances (see also [⁵]). Data required in addition to the basic toxicological data set for a well-substantiated risk analysis are given exemplarily for plant constituents and extracts in [⁶]. A decision tree included in this publication assists in identifying fundamental data needed for safety assessment. An extended proposal for a decision tree to assess the safety of food supplements is presented by the SKLM for discussion in Annex III. As suggested there, individual substances relevant for safety evaluation that are structurally characterized may be prioritized applying the TTC (Threshold of Toxicological Concern) concept [⁷].

In addition, the European Council has issued a guideline for the evaluation of plant-based food supplements [⁸] that addresses safety assessment aspects, issues concerning scientific substantiation of health-promoting effects as well as the

necessity for quality checks throughout the entire processing chain. This guideline can also be applied to food supplements containing material of animal origin. In this particular case, it is imperative that no high-risk material (e.g. from domestic animals with respect to BSE or other biological risks) is used.

4 Benefit evaluation

Proof for a health-promoting effect of the food supplement is the prerequisite for the desired claim. This claim should inform the consumer about properties of the product respectively of the active ingredient(s). It may refer to health-promoting effects and, in future, also to reduction of disease risk claims [9]. A claim is a narrative statement of the product-specific properties. It thus serves as the basis for the type and extent of the necessary data or studies that are to justify the claim. It must be adequately and scientifically substantiated according to the regulations in the German Law on Food and Feed (Lebensmittel- und Futtermittelgesetzbuch, LFGB) [10]. In particular, it also has to be adequately proven that the normal diet contains only insufficient quantities, if any, of the relevant substances comprised in the food supplement and that supplementing the diet with these substances makes sense.

The following additional publications can be used to clarify the procedure for the scientific substantiation of the health-promoting effects:

- Passclaim (Process for the Assessment of Scientific Support for Claims on Foods) [11, 12]
- Report of the Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases [13]
- SKLM criteria for the evaluation of functional foods: Safety aspects [2]

The SKLM is of the opinion that statements concerning reduction of disease risks should be substantiated on the basis of generally accepted scientific standards in accordance with *evidence-based medicine*³ [14]. The claimed effect must be proven for the individual product, particularly if interactions between various constituents of the food supplement cannot be excluded (e.g. effects on bioavailability).

After the product safety has been verified, it is generally necessary to carry out controlled human intervention studies according to currently recognised scientific standards in order to obtain scientific evidence for the health-promoting effect. Nature and extent of the necessary studies on humans must be individually specified

³ "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"

depending on the particular food supplement, on its postulated health-promoting effects and on the intended claim. Two independent studies are favoured; at least one clinical trial in humans is mandatory. It should be a controlled randomised double-blind trial, if possible.

The study design has to ensure that its aim can be accomplished reliably. In principle, such studies show basic parallels to those required for the authorization of a drug. Although nature and extent of the food supplement trials can be different from those for drugs, the quality regarding conceptual design, conduct and evaluation should not be of a lower standard than those used for drug authorization. They must be carried out on the basis of generally accepted scientific criteria and in accordance with the currently valid scientific quality standards. Likewise, the same ethical principles used for human studies, including GLP (good laboratory practice) and GCP (good clinical practice) compliance must be followed [^{15, 16}]. The study design has to ensure that adverse effects will also be recorded.

5 Conclusions and recommendations

"Other substances" are consumed in food supplements in a concentrated or isolated form and they cannot a priori be assumed to be harmless.

The Senate Commission therefore requires that

- before a food supplement is placed on the market, its safety must be proven according to the fundamental principles presented herein, also with respect to potential risk groups, and that
- the postulated benefits have to be proven as well, according to the principles set forth here.

Furthermore, the Senate Commission is also of the opinion that the preparation of a list of "other substances with a nutritional or physiological effect" that have already received approval for use in a food supplement (positive list) is a particularly effective tool to safeguard consumer health and safety at the European and international level.

To ascertain a sustainable consumer health protection the SKLM also recommends

- generation of consumption data for an exposure assessment and
- establishment of an alert system for suspected cases of undesired effects by food supplements (food supplement vigilance).

6 Literature

- ¹ Dietary Supplements: A Framework for Evaluating Safety, Committee on the Framework for Evaluating Safety of Dietary Supplements, Food and Nutrition Board, Institute of Medicine and National Research Council of the National Academies, National Academies Press, Washington, D.C. 2004
- ² Scientific Committee on Food, Guidance on submissions for food additive evaluations (Opinion expressed on 11 July 2001)
- ³ Scientific Committee on Food, Guidance on submissions for safety evaluation of sources of nutrients or of other ingredients proposed for use in the manufacture of foods (Opinion expressed on 11 July 2001)
- ⁴ Kriterien zur Beurteilung Funktioneller Lebensmittel: Sicherheitsaspekte. Symposium/Kurzfassung. Mitteilung 6; Senatskommission zur Beurteilung der gesundheitlichen Unbedenklichkeit von Lebensmitteln (Editor) Wiley-VCH Verlag, Weinheim, 2004
- ⁵ Higher Administrative Court of North-Rhine Westfalia from 10.11.2005 - 13 A 463/03, 9 K 740/99
- ⁶ Schilter B, Andersson C, Anton R, Constable A, Kleiner J, O'Brien J, Renwick AG, Korver O, Smit F, Walker R, Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements, *Food Chem Toxicol*, 41 (2003), 1625–1649
- ⁷ Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Wurtzen G; European branch of the International Life Sciences Institute. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem Toxicol*, 42 (2004), 65-83. Review
- ⁸ Council of Europe, Guidelines on the Quality, Safety and Marketing of Plant-Based Food Supplements, 24.06.2005
- ⁹ Regulation (EC) No 1924/2006 of the European Parliament and of the Council from 20.12.2004 on nutrition and health claims made on foods, Official Journal of the European Union, L12/3-L12/18
- ¹⁰ Law on Food and Feed, §11 (1) 2
- ¹¹ Aggett PJ, Asp N-G, Contor L, Cummings JH, Howlett J, Mensink RP, Prentice A, Rafter J, Riccardi G, Richardson DP, Saris WHM, Westenhoefer J, Passclaim (Process for the Assessment of Scientific Support for Claims on Foods) ILSI Europe (2005) ISBN 1-57881-197-X
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- ¹³ Report of the Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases, WHO Technical Report Series 916 (2003)

- ¹⁴ Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: Evidence based medicine: what it is and what it isn't. BMJ, 13; 312(7023) (1996), 71-72
- ¹⁵ Directive 2004/10/EC of the European Parliament and of the Council on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances from 11 February 2004, OJ No. L 50 p. 44
- ¹⁶ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use from 4 April 2001, Official Journal of the European Communities L 121: 35-44

Annex I: Glossary

Medicinal products Directive 2004/27/EC from 31.03.2004 defines a medicinal product as being any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [¹]. This Directive was implemented into German law in the German Medicinal Products Act [²].

Extracts are generally mixtures of substances that have been obtained by selective enrichment of characteristic constituents from a starting material by the use of (extraction) solvent(s) (other techniques may also be used). Plant extracts are obtained from plants or parts thereof that are in a processed or unprocessed condition [³].

Functional foods were originally developed in Japan where they can be placed on the market after obtaining an approval as "Foods for Specified Health Use (FOSHU)" [⁴]. There is currently no legally binding definition for functional foods (FF) in Europe. According to an EU initiative (consensus documents from the so-called FUFOSE working group [⁵]) a food can be regarded as being "functional" if, in addition to adequate nutritional and physiological effects, it has a demonstrable positive effect on one or more target functions in the body and is retailed exclusively as a foodstuff and not like a food supplement in a form similar to a medicinal product.

Foods means any substance or products, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans [⁶]. This does not include e.g. medicinal products (see above).

Novel foods are regulated in the EU by Regulation (EC) No. 258/97 on novel foods and novel food ingredients (in the so-called Novel Food Regulation) [⁷]. This applies to foods and food ingredients that were not used for human consumption to a significant degree in the European Union prior to the deadline of 15.05.1997 (date this regulation came into force). This includes foods and food ingredients with a new or intentionally modified primary molecular structure, foods and food ingredients consisting of or isolated from microorganisms, fungi or algae as well as foods and food ingredients that have been obtained by a process not currently used, where that process gives rise to significant changes in their composition or structure. Foods and food ingredients containing genetically modified organisms (GMO), consist of GMO or produced from GMO but which no longer contain them are no longer regulated by the Novel Food Regulation, effective from 7 November 2004, but are regulated from 18 April 2004 effective by Regulation (EC) No. 1829/2003 concerning genetically modified food and feed as well as Regulation (EC) No. 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC.

Food supplements are defined in Directive 2002/46/EC [⁸] from 10.06.2002 on the approximation of the laws of the Member States relating to food supplements. This Directive was implemented into German law with the "Ordinance on Food Supplements" [⁹] on 24.05.2004. A food supplement is defined in this ordinance as a foodstuff that is intended to supplement the general diet and which is a concentrate of nutrients or other substances with a nutritional or physiological effect on their own or in combination. Food supplements are marketed in dosed quantities, particularly in the form of capsules, pastilles, tablets, pills and similar pharmaceutical forms of liquids and powders that can be administered in small measured quantities. According to this Ordinance, only vitamins, minerals and trace elements are "nutrients" [⁸].

Annex II: Principles of Safety Analysis

Food safety should be assessed following established principles [¹⁰, ¹¹]. A safety assessment includes the following individual elements (for more information on the formal structure of a safety assessment, see [¹²]).

Product characterisation

The assessment of a food supplement includes the identification and adequate characterisation of the constituent(s), i.e. a description of the chemical composition, the physico-chemical, biological and/or microbiological properties as well as a description of the origin, isolation or manufacturing process. Furthermore, the specification, purity criteria and feasible analysis methods must be presented. Also required are information on possible degradation products, possible interactions with nutrients and any factors affecting their bioavailability.

Risk identification

Possible health risks or undesirable effects of the relevant ingredients in the food supplement must be identified using conventional studies:

- Toxicology / pharmacokinetics (intake, distribution, metabolism, excretion)
- Toxicity studies
- Studies on undesirable microbiological effects (pathogenicity, infectiousness, e.g. in the assessment of probiotic bacteria)

Hazard characterisation

In a hazard characterisation, the toxicological effects of relevant constituents that are to be used in the food supplement are assessed quantitatively or semi-quantitatively. The key objective of a hazard characterisation is to determine the dose-response relationship of relevant constituents and to assess the results with respect to their relevance to humans.

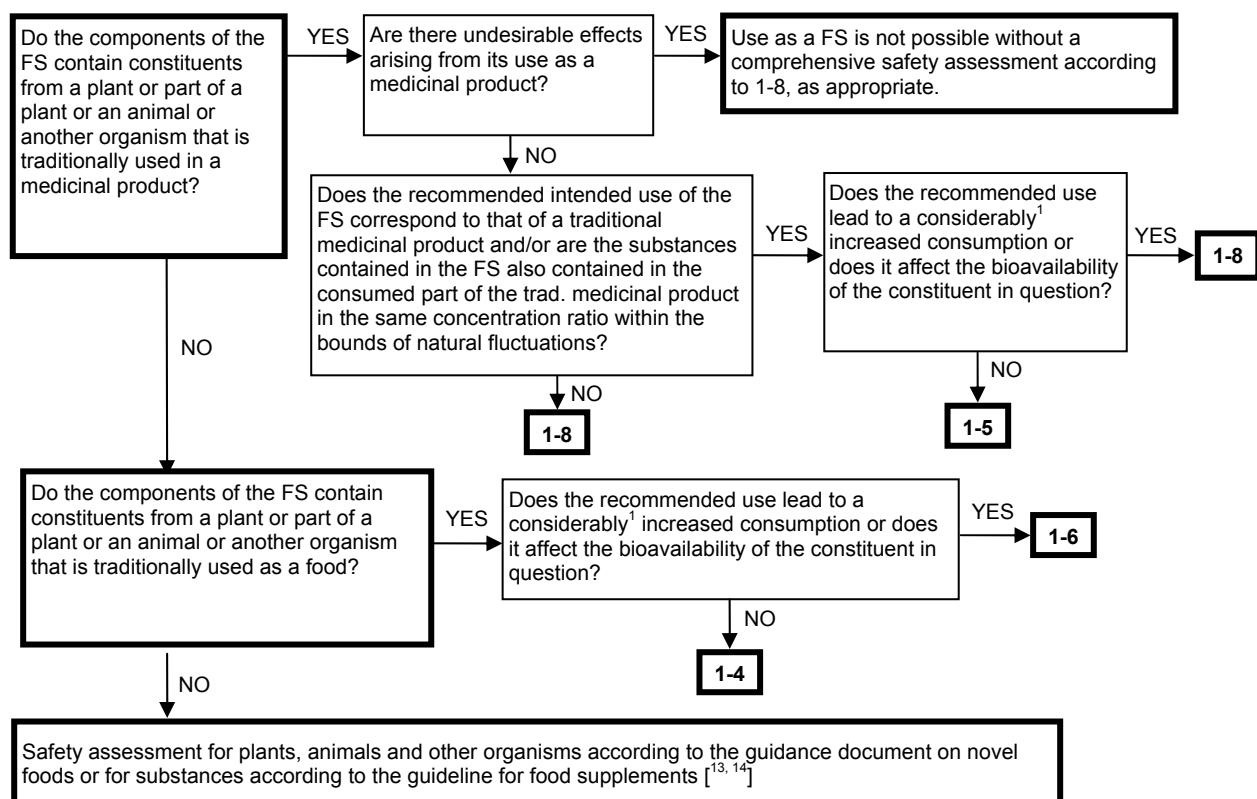
Exposure assessment

An exposure assessment includes a quantitative estimation of the probable intake of a substance from all major sources (including foods, medicinal products and a possible multiple intake from several products available on the market). The type of exposure with respect to time must also be considered, e.g. continuous or intermittent.

Risk characterisation

A risk characterisation estimates the probability of the substance or product having a potential adverse effect on the health at the calculated or estimated exposure levels on the basis of dose-response relationships.

Annex III: Proposal for a decision tree to identify the necessary data to be used as basis for a safety assessment of a food supplement (FS) containing "other substances with nutritional or physiological effects".



1	Identification of the organism used as the source (species, family, genus, wild or cultivated plant, part of the organism used as the source, provenance, etc.)
2	Specification of the organism used as the source or analyses of the constituents. Stipulation of the scientifically substantiated specification of the product with respect to natural variations in the physiologically / toxicologically, and if appropriate, pharmacologically relevant constituents and of the purity
3	Process description. Good agricultural practice (listing of used pesticides or medicinal products, storage, drying, traceability, etc.) as well as good manufacturing practice, technical details on processing, stability of the formulation
4	Exposure assessment for the target population and potential risk groups with respect to the relevant constituents resulting from consumption of the food supplement and from other sources
5	Evaluation of the properties. Scientifically substantiated ... <ul style="list-style-type: none"> • assessment of the nutritional and physiological properties of the relevant constituents • assessment of the toxicological, and if appropriate, pharmacological properties of the relevant constituents • assessment of the influence of the relevant constituents on the bioavailability and on the effect of other food constituents or medicinal products • assessment of the effect of other food constituents or medicinal products on the bioavailability and on the effect of the physiologically, toxicologically, and if appropriate, pharmacologically relevant constituents
6	Necessary studies. The extent and nature of studies to determine the safety of the relevant constituents or of the food supplement itself must be specified on a case-by-case basis. Such a case-by-case assessment should be carried out taking into account any prior knowledge from its previous use. The TTC (Threshold of Toxicological Concern) concept can be used to evaluate individual substances that have been structurally characterised ^[15] . It may be necessary to carry out supplementary studies (teratogenicity, reprotoxicity, specific periods of life, particularly sensitive groups of people).
7	Clinical studies. Human data on the variability of the physiological effect, compatibility, contraindications, etc.
8	Supplementary studies (pharmacokinetics, studies on the mechanism of action, etc.)

¹ As a rule, the decision as to whether consumption has considerably increased must be made on a case-by-case basis, depending on the respective constituent. For example, exceeding the 95th percentile of the consumption from a traditional use could be used as a criterion

Annex IV: Literature cited in the Annex

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- 2 German Medicinal Products Act, "Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394;), zuletzt geändert durch Artikel 30 des Gesetzes vom 26. März 2007 (BGBl. I S.378)"
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- 5 Diplock AT, Aggett PJ, Ashwell M, Bornet F, Fern EB, Roberfroid MB (1999) Scientific Concepts of Functional Foods in Europe: Consensus Document. British Journal of Nutrition 81 Suppl. 1
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- 7 Regulation (EC) No. 258/97 of the European Parliament and of the Council from 27 January 1997 concerning novel foods and novel food ingredients (OJ EC No. L 43 p.1), last amended by Regulation (EC) No. 1882/2003 from 29. 09.2003. (OJ EC No. L 284 p. 1)
- 8 Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (OJ EC No. L183 p. 51)
- 9 Ordinance on Food Supplements and the Amendment to the Ordinance on Vitaminised Foods from 24 May 2004 (Federal Law Gazette. I, p. 1011)
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- 14 Scientific Committee on Food, Guidance on submissions for food additive evaluations (Opinion expressed on 11 July 2001)
- 15 Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Wurtzen G; European branch of the International Life Sciences Institute. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol, 42 (2004), 65-83. Review