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SCIENTIFIC OPINION

Guidance for the preparation of dossiers for sensory additives[1†¥]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

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This guidance document follows the structure and definitions of Regulation (EC) No 1831/2003 and its implementing rules (Regulation (EC) No 429/2008). It is intended to assist the applicant in the preparation and the presentation of its application, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003. This document does not substitute for the obligation of an applicant to comply with the requirements of Regulation (EC) No 1831/2003 and its implementing rules.

A sensory additive is any substance, the addition of which to feed improves or changes the organoleptic properties of the feed, or the visual characteristics of the food derived from animals. The category 'sensory additives' is further grouped into two functional groups (Annex I of Regulation (EC) No 1831/2003):

(a) colourants:

  (i) substances that add or restore colour in feedingstuffs;

  (ii) substances which, when fed to animals, add colours to food of animal origin;

  (iii) substances which favourably affect the colour of ornamental fish or birds;

(b) flavouring compounds: substances the inclusion of which in feedingstuffs increases feed smell or palatability.

[1] On request from EFSA, Question No EFSA-Q-2010-01157, adopted on 14 December 2011.

[†] Parts in italics are coming from Regulation (EC) No 429/2008.

[¥] This guidance document replaces the previous EFSA Guidance for the preparation of dossiers for sensory additives, adopted on 14 October 2009. Revised on 12 November 2009 (EFSA-Q-2009-00832). The following sections have been updated: Part 1: Section 2, 3.1, 3.2 and 3.3; Part 2: Section 2, 3.2.2 and 3.3.

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THE TECHNICAL DOSSIER – GENERAL ASPECTS

The dossiers must enable an assessment to be made of additives based on the current state of knowledge and permit verification of the compliance of these additives with the fundamental principles for authorisation, which are laid down in Article 5 of Regulation (EC) No 1831/2003.

The studies to be submitted and the extent of them will depend on the additive nature, the functional group, the substance itself, the target animals and the conditions of use. The applicant should refer to Regulation (EC) No 429/2008 in order to evaluate which studies and information should be submitted with the application.

Reasons must be given for the omission from the dossier of any data prescribed there.

The dossier shall include detailed reports of all the studies performed, presented in accordance with the numbering system proposed in Regulation (EC) No 429/2008. The dossier shall include references and copies of all published scientific data mentioned and the copies of any other relevant opinions which have already been produced by any recognised scientific body. Where these studies have already been evaluated by a European scientific body following the legislation in force in the European Union, a reference to the result of the evaluation should be sufficient and a copy should be provided. *Data from studies that have been conducted and published previously or coming from peer review should clearly refer to the same additive as the one subject to the application for authorisation.*

Studies, including those that have been conducted and published previously or coming from peer review, shall be performed and documented according to appropriate quality standards (e.g., good laboratory practice (GLP) in accordance with Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 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 or International Organization for Standardization (ISO).

Where in vivo or in vitro studies are carried out outside the European Union, the applicant shall demonstrate that the facilities concerned comply with the Organisation for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice or ISO standards.

The determination of physico-chemical, toxicological and eco-toxicological properties must be performed in accordance with the methods established by Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, as last amended by Commission Directive 2004/73/EC, or with updated methods recognised by international scientific bodies. The use of methods other than these must be justified.

The studies involving animals should respect the rules on animal welfare laid down by European Union legislation, particularly those listed in Directive 63/2010/EC and they should not be repeated if not necessary. *The use of in vitro methods or of methods refining or replacing the usual tests using laboratory animals or reducing the number of animals used in these test should be encouraged. Such methods should be of the same quality and provide the same level of assurance as the method they aim to replace.*

The description of the methods of analysis in feed or water shall be in conformity with the rules of Good Laboratory Practice (GLP) as laid down in Directive 2004/10/EC and/or EN ISO/IEC 17025. These methods shall comply with the requirements laid down in Article 11 of Regulation (EC) No 882/2004 of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules.

Each dossier shall contain a public summary and a scientific detailed summary in order to enable the additive concerned to be identified and characterised and a labelling proposal as referred to in Article 7(3)(e) of Regulation (EC) No 1831/2003.

A post-market monitoring proposal should be proposed only for those additives which consist of, contain or are produced from genetically modified organisms as required by Article 7(3)(g) of Regulation (EC) No 1831/2003.

1. SECTION I: SUMMARY OF THE DOSSIER

1.1 Public summary according to Article 7(3)(h) of Regulation (EC) No 1831/2003

The applicant shall submit a summary indicating the main features of the additive concerned. The summary shall not contain any confidential information and shall be structured as follows:

1.1.1 Contents

a) name of the applicant(s);
b) identification of the additive;
c) method of production and method of analysis;
d) studies on safety and efficacy of the additive;
e) proposed conditions for use; and
f) proposal for post-market monitoring.

1.1.2 Description

a) name and address of the applicant(s)

This information shall be provided in all cases. *When a dossier is submitted by a group of applicants, the name of each of them should be indicated.*

b) identification of the additive

The identification of the additive shall contain a summary of the information required according to Annex II and III of Regulation (EC) No 429/2008, depending on the type of the feed additive authorisation. In particular: name of the additive, proposed classification by category and functional group, target species/animal categories and doses.

c) method of production and method of analysis

The manufacturing process shall be described.

The general procedures of the analytical methods to be used for the analysis for the official controls of the additive as such, in premixtures, and in feedingstuffs, as required in Annex II and III of Regulation (EC) No 429/2008 shall be described. If appropriate, on the basis of the information submitted, the procedure of the method(s) to be used for the analysis for the official controls of the additives or its metabolites in food of animal origin should be included.

d) studies on safety and efficacy of the additive

The conclusion regarding the safety and efficacy of the additive based on the different studies performed shall be given. The results of the studies may be included in a tabular form to support the conclusion of the applicant(s). Only studies required according to Annex III of Regulation (EC) No 429/2008 shall be indicated in the summary.

e) proposed conditions for use

The proposal for conditions of use shall be provided by the applicant(s). In particular the applicant shall describe the level of use in water or feed, together with the detailed conditions of use in complementary feedingstuffs. Information is also required where other methods of administration or incorporation in feed or water are used. Any specific conditions for use (e.g. incompatibilities), specific labelling requirements and animal species for which the additive is intended shall be described.

f) proposal for post-market monitoring

This part is only required for additives falling within the scope of European Union legislation relating to the marketing of products consisting of, containing or produced from GMOs.

1.2 Scientific summary of the dossier

A scientific summary including details of each part of the documents submitted to support the application shall be submitted. This summary shall include the conclusions made by the applicant(s).

The summary must follow the order of Annex II of Regulation (EC) No 429/2008 and address all the different parts with reference to the relevant pages of the dossier.

1.3 List of documents and other particulars

The applicant must identify the number and titles of volumes of documentation submitted in support of the application. A detailed index with reference to volumes and pages shall be added.

1.4 List of parts of the dossier requested to be treated as confidential, where necessary

The list shall make reference to the relevant volumes and pages of the dossier.

PART 1 - COLOURANTS

2. SECTION II: IDENTITY, CHARACTERISATION AND CONDITIONS OF USE OF THE ADDITIVE; METHODS OF ANALYSIS.

The additive has to be fully identified and characterised. For the majority of sensory additives, which are not subject to a specific holder of the authorisation, the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply. For those sensory additives subject to a specific holder of the authorisation (i.e., additives falling within the scope of European Union legislation relating to the marketing of products consisting of, containing or produced from GMOs), the whole Section II applies (follow the section II of the guidance for zootechnical additives).

The studies described in this section must be based on the final product(s) for which authorisation is sought. In-house identifiers should be avoided unless embedded in third-party documents. In this case a statement is required to confirm that the identifier(s) refers to the formulation(s) for which the claim is made.

2.1 Identity of the additive

For many colourants there is no distinction between the active substance and the additive, particularly for those substances that add or restore colour to feedingstuffs.

2.1.1 Name of the additive

The name of the additive (characterisation of the active substance(s) as defined in the subsection 2.2.1) should be given.

2.1.2 Proposal for classification

In addition to the classification "sensory additive/colourant" and its respective subgroup, a proposal for the classification of the additive for additional categories[4] and functional groups

[4] If the applicant applies for one or more categories in addition to sensory additives, reference should be made to the relevant guidance document(s).

according to its main functions under Article 6 and Annex I of Regulation (EC) No 1831/2003 can be made.

Any other authorisation as feed or food additive, veterinary drug or other kind of authorisations of the active substance has to be specified and properly referenced. Data from other known uses of the identical active substances must be provided.

2.1.3 Qualitative and quantitative composition (active substance, other components, impurities, batch to batch variation)

The active substance(s) and all other components of the additive should be listed, giving the proportion by weight in the final product.

The applicant should provide a specification of the product as it relates to the active substance(s)/agent(s). Evidence should be provided by the analysis of at least five production batches that this specification is satisfied in practice. Certificates of analysis indicating exact values should be attached. Statements of compliance alone are not considered sufficient.

If the active component of the additive is a mixture of active substances, each of which is clearly definable (qualitatively and quantitatively), the active substance(s) must be described separately and the proportions in the mixture given.

Without prejudice to any request for supplementary information made by the EFSA according to Article 8(2) of Regulation (EC) No 1831/2003, the applicant may omit the description of other components with no safety concerns other than active substances or agents for additives not within the scope of Regulation (EC) No 1829/2003.

2.1.4 Purity

The applicant *shall* identify and quantify microbial and chemical (including residual solvents) impurities, substances with toxic or other undesirable properties that are not intentionally added and do not contribute to the activity of additive. Any substances produced via fermentation should be free of antimicrobial activities relevant to the use of antibiotics in humans or animals. In addition the absence of production organisms in the additive should be confirmed.

The protocol used for the routine screening of production batches for contaminants and impurities shall be described and appropriate action levels should be defined.

All the data provided have to support the proposal for a specification of the additive. Evidence should be provided by the analysis of at least three production batches that this specification is satisfied in practice. Certificates of analysis indicating the exact values should be provided. Statements of compliance alone are not considered sufficient. The limit of quantification (LOQ) of the method should be given when the results are expressed as less than a given value.

Monitoring for contaminants and impurities should be consistent with existing legislation (e.g. Directive 2002/32/EC, or specifications from European Union food additive authorisations) and recommendations from internationally recognised sources when these are available (e.g. Joint FAO/WHO Expert Committee on Food Additives (JECFA) specifications; Commission recommendation on the presence of deoxynivalenol, zearalenone, ochratoxin A, T-2 and HT-2 and fumonisins in products intended for animal feeding). Additional measures should be introduced following the HACCP analysis of the specific process, as necessary.

As a guide the following should be considered as minimum requirements:

– for fermentation/cultivation products: microbiological contamination (*Salmonella*, enterobacteriaceae, total yeasts and filamentous fungi), and, depending on the fermentation media and excipients, mycotoxins,[5] heavy metals (Pb, Hg, Cd) and arsenic. *The extent to which spent growth medium is incorporated into the final product* shall *also*

[5] The selection of mycotoxins for analysis should be made according to the different matrices, where appropriate.

be indicated. For fermentation products produced by genetically modified microorganisms (GMM), identification and quantification of recombinant DNA in the final product should be provided.

- for plant derived substances: microbiological and botanical contamination (e.g., castor oil plant, weed seeds, rye ergot in particular), mycotoxins, dioxins and dioxin-like PCBs, pesticides,[6] and, where appropriate, substances of toxicological concern known to occur in the original plant;
- for animal derived substances: microbiological contamination, heavy metals and arsenic;
- for mineral substances: heavy metals and arsenic, dioxins and dioxin-like PCBs;
- *for products produced by chemical synthesis and processes: all chemicals used in the synthetic processes and any intermediate products remaining in the final product should be identified and their concentrations given.*

The current maximum levels set for residual solvents used in veterinary drugs (VICH guidance GL18) should not be exceeded.

2.1.5 Physical state of each form of the product

EFSA recommends the provision of dusting potential (triplicate analysis) for solid preparations representative of the form(s) likely to be marketed to allow an assessment of respiratory exposure for users. Depending on the outcome of these studies and the nature of the substance, further investigations (e.g. particle size distribution in dust) may become necessary.

For liquid preparations, data on vapour pressure, specific weight and where the additive is intended to be used in water, solubility or dispersability should be provided.

The same data should be provided for feed additives already authorised as food additives for which a detailed assessment of user safety was not performed.

2.2 Characterisation of the active substance(s)

2.2.1 Description

A qualitative description of the active substance(s) should be given. This should include purity and origin of the substance(s), plus any other relevant characteristics.

2.2.1.1 Chemical substances

Chemically well-defined substances should be described by generic name, chemical name according to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, other generic international names and abbreviations and/or Chemical Abstract Service (CAS) Number. The structural and molecular formula and molecular weight must be included. Where relevant, data on isomeric forms and accompanying structurally related compounds should be included.

For additives of plant origin the information required under section 2.2.2.1 of the guidance for sensory additives/flavouring compounds should be provided. The constituent(s) contributing to the claimed effects should be identified. The phytochemical marker(s) characteristic of the plant of origin must be included.

The microbial origin (bacteria, yeasts, filamentous fungi and micro-algae) of colourants produced by fermentation/cultivation should be described and any history of modification of the production organism should be indicated. It should be clearly stated whether the microorganism is genetically modified or not within the meaning of the legislation (Directive 2001/18/EC). *The name and taxonomic classification of each microorganism shall be*

[6] Residues specified under the undesirable substances directive (Directive 2002/32/EC) and any other pesticide residues of potential concern to target animals and/or consumer safety.

provided, according to the latest published information in the International Codes of Nomenclature (ICN). Microbial strains shall be deposited in an internationally recognised culture collection (preferably in the European Union) and maintained by the culture collection for the authorised life of the additive. A certificate of deposition from the collection, which shall specify the accession number under which the strain is held, must be provided.

2.2.2 Relevant properties

2.2.2.1 Chemical substances

Description of physical and chemical properties should be given. Dissociation constant, pKa, electrostatic properties, melting point, boiling point, density, vapour pressure, solubility in water and in organic solvents, K_{ow} and K_d/K_{oc}, mass spectrometry and absorption spectra, NMR data and any other relevant physical properties should be provided where appropriate.

2.2.2.2 Microorganisms (as source of the additive)

Microorganisms used as a production strain should not be capable of producing antibiotic substances that are relevant to antibiotics in human and veterinary medicine.

Strains of microorganisms belonging to a taxonomic group that includes members known to be capable of producing toxins or other virulence factors shall be subject to appropriate tests to demonstrate at a molecular and, if necessary, cellular level the absence of any cause for concern. As an example on how to assess the potential for toxin production see the technical guidance on the assessment of the toxigenic potential of *Bacillus* species used in animal nutrition.

2.3 Manufacturing process, including any specific processing procedures

To define the critical points of the process that may have an influence on the purity of the active substance or additive a detailed description of the manufacturing process shall be given.

2.3.1 Active substance(s)

A description of the production process (e.g., chemical synthesis, fermentation, cultivation, extraction from organic material or distillation and downstream purification steps) used in the preparation of the active substance(s) of the additive should be submitted, if appropriate by means of a flowchart. *The composition of the fermentation/cultivation media should be provided.* For GMMs used as source of additives and grown under contained conditions, Directive 90/219/EC applies.

2.3.2 Additive

A detailed description of the manufacturing process of the additive should be submitted. The key stages in the preparation of the additive including the point(s) of introduction of the active substance(s) and other components, and any subsequent process steps affecting the additive preparation should be provided, if appropriate by means of a flowchart. A material safety data sheet (MSDS) must be provided for all components of the additive.

2.4 Physical-chemical and technological properties of the additive

2.4.1 Stability

Stability is assessed through the persistence of the active substance (or rarely by the persistence of colour in feedingstuffs). Data should include at least observations at the beginning and end of the storage period.

Where there is a loss of stability, measured by the analytical follow-up of the active substance, potential degradation or decomposition products should be characterised, where appropriate.

Stability studies are not required for metal oxides and carbon black used as colorants.

2.4.1.1 Shelf-life of the additive

The expected shelf-life of the additive as marketed should be proposed, based on data from studies performed under the recommended storage conditions, which should be specified. Data should be provided from at least three batches of the additive. The composition of the additive used must be described.

2.4.1.2 Stability of the additive used in premixtures and feedingstuffs

The stability of the additive at the recommended inclusion level normally should be studied in feedingstuffs manufactured and stored under practical conditions, and if relevant, in premixtures.

Stability should be tested preferably in a premixture containing trace elements; otherwise the additive should be labelled as "not to be mixed with trace elements". The quantitative and qualitative composition of the premixtures should be given. Stability studies in premixtures should be of at least six months' duration, and should be based on three batches of the additive.

Stability in feedingstuffs should be assessed in both mash and further processed feed (e.g., pelleted or extruded, including the influence of the respective processing). Data provided should cover a representative range of feedingstuffs (at least three) relevant to the use of the additive, but can be based on a single batch of the additive. The quantitative and qualitative composition of the feedingstuffs used for the studies should be given. Stability studies in feedingstuffs should be of at least three months' duration.

2.4.1.3 Stability of the additive used in water

The stability of the additive intended to be distributed via water for drinking should be studied under conditions simulating practical use (e.g., environment and water temperature, time) for a minimum duration of 48 h. These data should also take into consideration the presence of excipients that could trigger growth of contaminant microorganisms.

2.4.2 Homogeneity

The capacity for homogeneous distribution of the feed additive in premixtures, feedingstuffs or water must be demonstrated, as appropriate. The same criteria as described under 2.4.1 should be used. As a guide, a minimum of ten sub-samples (10 – 20 g) from a single batch (of the premixture or feedingstuff) should be analysed and the coefficient of variation calculated. If homogeneity is demonstrated in the final feedingstuff, there is no need to demonstrate homogeneity of mixing at any preceding stages in feed production (including premixtures).

Statistical considerations[7] as a substitute for analytical data from subsamples will not be considered.

For additives intended to be distributed via water for drinking, homogeneity studies are only required when the active substance is not fully soluble at its proposed concentration of use. In those cases, sampling should take into consideration conditions of use and may require sampling at different locations (where the animal has access to the additive) and time points. Samples from a minimum of ten locations per time point should be analysed and the coefficient of variation calculated.

Homogeneity studies are not required for substances that add or restore colour to feedingstuffs.

2.4.4 Physico-chemical incompatibilities in feed

Physico-chemical incompatibilities or interactions that could be expected in feed with feed materials, carriers, other approved additives, or medicinal products must be documented.

[7] For example, Jansen HD. (1992) Mischtechnik im Futtermittelbetrieb. Die Mühle + Mischfuttertechnik. 129 (20), 265-270.

2.5 Conditions of use of the additive

2.5.1 Proposed mode of use in animal nutrition

The proposed use in feed should be defined. *The animal species or categories, age group or production stage of animals shall be indicated,* as appropriate, *in accordance with the categories listed in Annex IV of Regulation (EC) No 429/2008. Possible contra-indications shall be mentioned.*

For additives intended to favourably affect the colour of ornamental fish or birds or that add or restore colour in feedingstuffs, the recommended levels of inclusion in complete feedingstuffs should be provided.

For additives which, when fed to animals, add colours to food of animal origin, details of the proposed method of administration, the proposed dose range, including a maximum content in the complete feedingstuff and the proposed duration of administration must be provided. If a particular use in complementary feedingstuffs for some animal species or categories is intended, the (daily) dose should be proposed and justified.

For additives intended to be used in water for drinking, the concentrations derived from feed use should follow the considerations in paragraph 2.3 of the technical guidance on tolerance and efficacy studies.

2.5.2 Information related to worker safety

2.5.2.1 Chemical substances

A material safety data sheet formatted in accordance with the requirements of Commission Directive 91/155/EEC[8] of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC as amended by Directive 2001/58/EC must be provided. If necessary, measures for the prevention of occupational risks and means of protection during manufacture, handling, use and disposal shall be proposed.

2.5.2.3 Labelling requirements

Without prejudice to the labelling and packaging provisions laid down in Article 16 of Regulation (EC) No 1831/2003, any specific labelling requirements and, where appropriate, specific conditions for use and handling (including known incompatibilities and contraindications) and instructions for proper use shall be indicated.

2.6 Methods of analysis and reference samples

Methods of analysis to determine the active substance in the additive itself and in premixtures and feedingstuffs as appropriate should be submitted. These should be suitable for the official control of the feed additive. If there are residues of concern, a method of analysis of the active substance and/or its metabolites (including the marker residue) in the relevant tissues/products should be provided.

These methods will be evaluated by the European Union Reference Laboratory (EURL). Details of the requirements are specified in the Regulation (EC) No 429/2008. Applicants should refer to the guidance provided by the EURL**.**

Methods to determine the identity and the characteristics of the additive (composition of the additive, impurities, physical and chemical properties) should be internationally recognised or otherwise fully described.

3. SECTION III: STUDIES CONCERNING THE SAFETY OF THE ADDITIVE

The studies included in this section are intended to permit assessment of:

[8] Repealed by Regulation (EC) No 1907/2006.

- *the safety of use of the additive in the target species;*
- *any risk associated with the selection and/or transfer of resistance to antimicrobials and increased persistence and shedding of enteropathogens;*
- *the risks to the consumer of food derived from animals given feedingstuffs containing or treated with the additive or which could result from the consumption of food containing residues of the additive or its metabolites;*
- *the risks from respiratory, other mucosal tissue, eye or cutaneous contact for persons likely to handle the additive as such or as incorporated into premixtures or feedingstuffs; and*
- *the risks of adverse effects on the environment, from the additive itself, or products derived from the additive, either directly and/or excreted by animals.*

Where an additive has multiple active components, each may be separately assessed for safety for consumers and then consideration given to additivity (exclusion of interactions). Alternatively, the complete mixture should be assessed.

3.1 Studies concerning the safety of use of the additive for the target animals

3.1.1 Tolerance for the target species

The aim of the tolerance test is to provide a limited evaluation of short-term toxicity of the additive to the target animals. It is also used to establish a margin of safety, if the additive is consumed at higher doses than recommended.

All studies reported in this section must be based on the additive described in Section II, except in cases where a concentrated form of the additive is recommended to be tested.

A tolerance study in the relevant target species/category is required for substances which, when fed to animals, add colour to food of animal origin.

For substances that add or restore colour in feedingstuffs and for substances which favourably affect the colour of ornamental fish or birds, safety for the target animals could be demonstrated with studies performed on animals receiving the additive under the recommended conditions of use. Evidence can also be provided by reference to existing scientific literature.

For details on how to perform and report tolerance studies, see the technical guidance on tolerance and efficacy studies in target animals.

3.1.2 Microbial studies

Microbiological studies are not required for colourants intended to favourably affect the colour of ornamental fish or birds or intended to add colour to food of animal origin which are already authorised.

Studies are also not required for:

- compounds known or demonstrated not to posses an antimicrobial activity, or whose structure or physical properties preclude antimicrobial activity, at concentrations relevant to feed use; or
- additives which consist only of microorganisms considered by EFSA to qualify for the QPS approach to safety assessment.

Where required, studies should demonstrate that the additive does not induce cross-resistance to antibiotics used in human or veterinary medicine or encourage the growth and/or shedding of zoonotic agents.

For those additives that in the tolerance test give an indication of an adverse effect possibly related to digestive tract disturbances, studies on the effects on the target animal gastrointestinal microbiota are required.

For the details see the technical guidance on microbial studies.

3.2 Studies concerning the safety of use of the additive for consumers

The aim is to evaluate the safety of the additive for the consumer and to establish potential residues of the additive or its metabolites in food derived from animals given feed or water containing or treated with the additive. This section consists of metabolic and residue studies (3.2.1.), toxicological (*in vitro* and *in vivo*) studies (3.2.2) and the assessment of consumer safety (3.2.3).

Studies concerning safety for consumers are not required for:

- substances which favourably affect the colour of ornamental fish or birds.
- substances that add or restore colour in feedingstuffs that when fed to animals are essentially not absorbed and excreted unchanged (or if transformed in the digestive tract, its metabolites can be demonstrated to be essentially not absorbed).

For additives already authorised in food, refer to the technical guidance on additives already authorised in food.

For all other colourants, full section applies.

For details on how to assess consumer safety, refer to the technical guidance on consumer safety.

3.2.1 Metabolic and residue studies

The establishment of the metabolic fate of the additive in the target species is a determinant step in the identification and quantification of the residues in the edible tissues or products derived from the animals given the feed or water containing the additive.

For some additives, depending on their nature or use, it may not always be necessary to carry out metabolic and residues studies.

3.2.1.1 Metabolic studies

The purpose of metabolic studies is to evaluate the absorption, distribution, biotransformation and excretion of the additive in the target species and in a laboratory animal.

Metabolic studies are not required if the substance is naturally present in significant amounts in food or feedingstuffs or the substance is a normal constituent of body fluids or tissues.

For all other colourants, metabolic studies should be provided.

3.2.1.2 Residue studies

For colourants, the primary objective of residue data is to enable the estimation of consumer exposure.

Residue studies are required for all substances for which metabolic studies are needed.

Residue data for the parent compound and significant metabolites are required for all colourants which add colour to food of animal origin and for those substances that add or restore colour in feedingstuffs if the additive results in tissue/product retention in the target species. In such cases, the requirement is limited to the measurement of the tissue/product concentration (at steady state) in a group supplemented with the highest recommended dose in comparison to an untreated group.

3.2.2 Toxicological studies

The safety of the additive for the consumer is typically assessed on the basis of the toxicological studies performed *in vitro* and *in vivo* usually on laboratory animals.

Toxicological studies must be carried out with the active substance. If the active substance is present in a fermentation/cultivation product, this should be tested. The

fermentation/cultivation product tested must be identical to that to be used in the commercial product.

For xenobiotic substances (defined as chemicals which are not a natural component of the host organism), the complete set of toxicological studies described in the guidance for consumer safety is normally required.

Physiological substances (and in the case of colourants, which naturally occur in the diet) whose use results in much higher concentrations than usual in the host organism may be treated as xenobiotics. In these cases, the need for toxicological studies should be considered on a case by case basis, taking into account the level and nature of exposure.

In the case of colourants not of xenobiotic nature that are produced by fermentation/cultivation, the minimum requirement consists of genotoxicity/mutagenicity studies and a subchronic (90 day) oral toxicity study unless the colourant is produced by a microorganism considered by EFSA to qualify for the QPS approach to safety assessment (or rarely from a commercial strain (lineage) of microorganism with a substantial history of documented safe use).

For microorganisms used for the production of a sensory additive, the specific concerns in section 2.2.2.2 should always be addressed, as appropriate.

3.2.3 Assessment of consumer safety

In general, consumer safety is assessed by a comparison of the established health based reference value, such as the Acceptable Daily Intake (ADI) or Tolerable Upper Intake Level (UL) and calculated theoretical intake of the additive or its toxicologically relevant metabolites from food. For additives without a health based reference value, an estimate of toxicity should be established following 3.2.2.

3.3 Studies concerning the safety of use of the additive for users/workers

Workers can be exposed mainly by inhalation or topical exposure while manufacturing or handling or using the additive. Experience in the manufacturing plant is often an important source of information in evaluating the risks to workers from exposure to the additive itself by both airborne and topical routes.

User safety is established on the basis of a final formulation. However, once an active substance has been authorised as a sensory additive, different formulations can be placed on the market with reference to that authorisation. Consequently, not all forms of the product can be directly tested for user safety. For assessing the safety for the user of sensory additives, the active substance is the principal concern provided that other components do not introduce safety issues.

Therefore, assessment of user safety will be based on the available specific studies, the MSDS, and the nature of the active substance(s).

Additives with a high dusting potential or those used under circumstances which could generate aerosols are of particular concern. Any data on dusting potential will be used for exposure assessment. Additives of proteinaceous nature are assumed to be respiratory sensitisers.

Information on precautionary measures to be taken when handling the additive should be provided (see 2.5.2). *However, use of personal protective devices should only be regarded as a measure of last resort to protect against any residual risk once control measures are in place. It is preferable, for example, to consider reformulation of the product.*

For details on how to assess user/worker safety, refer to the technical guidance on user safety.

3.4 Studies concerning the safety of use of the additive for the environment

Administration of additives typically occurs over long periods, often involves large groups of animals and the active substance(s) may be excreted to a considerable extent either as the parent compound or its metabolites.

To determine the environmental impact of additives, a stepwise approach should be followed. All additives have to be assessed through Phase I to identify those additives which do not need further testing. For the other additives a second phase (Phase II) assessment is needed to provide additional information, based upon which further studies may be considered necessary.

The impact on the environment as a result of the Phase I assessment will be considered negligible if:

- the substance is a physiological/natural substance whose use will not result in a substantial increase in concentration in the environment; or
- the additive is intended for non food-producing animals only.

For additives produced by genetically modified microorganisms the specific requirements of the "Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use" should be satisfied.

For details on how to assess environmental safety, refer to the technical guidance on environmental risk assessment.

4. SECTION IV: STUDIES CONCERNING THE EFFICACY OF THE ADDITIVE

Studies should demonstrate the efficacy for each proposed use under the recommended conditions of use. *Such studies must permit the evaluation of the efficacy of the additive according to common farming practices in the EU.*

a) For substances which, when fed to animals, add colour to food of animal origin

The change in colour of products obtained from animals receiving the additive should be measured using the appropriate methodology (e.g., colour fan, reflectance spectroscopy). It should be demonstrated that the use of the additive does not adversely affect product stability or sensory and nutritional qualities of the food. Evidence of efficacy can be demonstrated in long term studies or, where the relationship between a particular substance and the colour of animal tissues/products is well documented, in short term studies (e.g., bioavailability).

For details on how to perform and report efficacy studies, see the technical guidance on tolerance and efficacy studies in target animals.

b) For substances that add or restore colour in feedingstuffs

Evidence of the efficacy of the additive should be demonstrated using laboratory-based studies by means of appropriate criteria as reflected in recognised acceptable methods in comparison with an appropriate control feed.

The studies should be designed to cover a representative range of feedingstuffs to which the additive will be applied. Results should be statistically evaluated and differences between groups accepted at $P \leq 0.05$. Non-parametric tests may be necessary when a low number of observations is available.

c) For substances which favourably affect the colour of ornamental fish and birds

Colour changes should be measured using the appropriate methodology. Evidence of efficacy may also be provided by other experimental studies (e.g., bioavailability) or by reference to scientific literature.

4.6 Studies on the quality of animal products where this is not the effect claimed

Evidence should be given that the additive does not have a negative effect or other unintended effect on the sensory and nutritional (and if appropriate, hygienic and technological) characteristics of food deriving from animals fed the treated feed.

Evidence can be based on physiological/metabolic considerations or given by reference to scientific literature. Specific studies may be necessary in case of substances for which residue studies are required. An unsupplemented group should be compared with a group receiving the highest dosage proposed for the additive. *The data should allow statistical evaluation.*

5. SECTION V: POST-MARKET MONITORING PLAN

A post-market monitoring plan is required only for sensory additives that are products consisting of, containing or produced from GMOs, in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effects resulting from the use of the additive on human or animal health or the environment, in accordance with the characteristics of the products concerned.

The design of the monitoring plan shall be detailed on a case-by-case basis and identify who (e.g., applicant, users) will carry out the various tasks that the monitoring plan requires, who is responsible for ensuring that the monitoring plan is set into place and carried out appropriately. The post-market monitoring plan should in all cases ensure that there is a route by which the competent control authorities, the Commission and the EFSA are informed of any observed adverse effects.

PART 2 – FLAVOURING COMPOUNDS

For the purpose of the evaluation of applications of these products, flavourings are classified in the following subgroups:

1. Natural products:
   1.1. Natural products - botanically defined.
   1.2. Natural products - non-plant origin.
2. Natural or corresponding synthetic chemically defined flavourings.
3. Artificial substances.

In general, in the case of the group 'natural products', whole plants, animals and other organisms and parts of these or products thereof resulting from very limited processing such as crushing, grinding or drying (e.g., many herbs and spices), shall not be considered as falling under the functional group flavourings of the category sensory additives.

If sufficient structural/metabolic similarity exists between flavouring compounds (e.g., there is already an established food flavouring group evaluation, FGE), a group-based application and evaluation can be performed.

Natural products (extracts) whose composition is well defined may be assessed on the basis of their major and characteristic components, taking into account any components of known toxicological concern. As a guide, all components representing more than 20% of the natural product solids should be considered as major components. However, in some cases, a lower concentration may apply.

2. SECTION II: IDENTITY, CHARACTERISATION AND CONDITIONS OF USE OF THE ADDITIVE; METHODS OF ANALYSIS.

The additive has to be fully identified and characterised. For the majority of sensory additives, which are not subject to a specific holder of the authorisation, the paragraphs 2.1.2, 2.1.3,

2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.4.1, 2.4.2, 2.4.4, 2.5 and 2.6 apply. For those sensory additives subject to a specific holder of the authorisation (i.e., additives falling within the scope of European Union legislation relating to the marketing of products consisting of, containing or produced from GMOs), the whole Section II applies (follow the section II of the guidance for zootechnical additives).

Because of the difficulty of identifying all of the active components in a natural product, the major/characteristic component(s) should be considered, for the purpose of this document, as the active substance(s).

The studies described in this section must be based on the final product(s) for which authorisation is sought. In-house identifiers should be avoided unless embedded in third-party documents. In this case a statement is required to confirm that the identifier(s) refers to the formulation(s) for which the claim is made.

2.1 Identity of the additive

It is recognised that for most flavourings there is no distinction between the active substance and the additive.

2.1.1 Name of the additive

A name of the additive should be proposed. This should reflect the production process and source or the active substance, as appropriate (see subsection 2.2.1).

2.1.2 Proposal for classification

In addition to the classification "sensory additive/flavouring compounds" a proposal for the classification of the additive for additional categories[9] and functional groups according to its main functions under Article 6 and Annex I of Regulation (EC) No 1831/2003 can be made.

The relevant subgroup (see above) to which the flavouring compound belongs must be indicated. In case the product does not fit into any of the above subgroups, this shall be mentioned and justified.

Any other authorisation as feed or food additive, veterinary use or other kind of authorisations of the active substance has to be specified and properly referenced. Data from other known uses of the identical active substances or agents also should be provided.

2.1.3 Qualitative and quantitative composition (active substance(s), other components, impurities, batch to batch variation)

The active substance(s) and the other components of the additive should be listed, giving the proportion by weight in the final product.

The applicant should provide a specification of the product as it relates to the active substance(s). Evidence should be provided by the analysis of at least five production batches that this specification is satisfied in practice. Certificates of analysis indicating exact values should be attached. Statements of compliance alone are not considered sufficient.

Natural products and artificial substances in which the constituents cannot be described by precise chemical formula (e.g. plant polymers, smoke flavourings[10]) and/or where not all can be identified should be characterised by the constituent(s) contributing to its activity and/or typical major constituent(s).

Without prejudice to any request for supplementary information made by the EFSA according to Article 8(2) of Regulation (EC) No 1831/2003, the applicant may omit the description of other components with no safety concerns other than active substances for additives not within the scope of Regulation (EC) No 1829/2003.

[9] If the applicant applies for one or more categories in addition to sensory additives, reference should be made to the relevant guidance document(s).

[10] As defined in Regulation (EC) No 1334/2008. OJ L 354, 31.12.2008, p. 34.

2.1.4 Purity

The applicant should identify and quantify microbial and chemical (including residual solvents) impurities, substances with toxic or other undesirable properties that are not intentionally added and do not contribute to the activity of additive. Any substances produced via fermentation should be free of antimicrobial activities relevant to the use of antibiotics in humans or animals and the absence of viable production organisms in the additive should be confirmed.

The protocol used for the routine screening of production batches for contaminants and impurities should be described and appropriate action levels should be defined.

The data provided should support a proposal for a specification of the additive. Evidence should be provided by the analysis of at least three production batches that this specification is satisfied in practice. Certificates of analysis indicating the exact values should be provided. Statements of compliance alone are not considered sufficient. The limit of quantification (LOQ) of the method should be given when the results are expressed as less than a given value.

Monitoring for contaminants and impurities should be consistent with existing legislation (e.g., Directive 2002/32/EC, or specifications from European Union food additive authorisations) and recommendations from internationally recognised sources when these are available (e.g., Joint FAO/WHO Expert Committee on Food Additives (JECFA) specifications; Commission recommendation on the presence of deoxynivalenol, zearalenone, ochratoxin A, T-2 and HT-2 and fumonisins in products intended for animal feeding). Additional measures should be introduced following the HACCP analysis of the specific process, as necessary.

Emphasis will be placed on the minimum assay value for the active substance(s) and the identification of any other components to 99% (w/w) of the additive.

As a guide the following should be considered:

– For all flavouring additives: process-related impurities (e.g., residual solvents, degradation products).

– For natural products and natural chemically defined compounds: carry-over of any compound of toxicological concern from the starting material, microbiological contamination, mycotoxins and pesticides,[11] heavy metals (Pb, Hg, Cd) and arsenic, dioxins and dioxin-like PCBs.

– for fermentation products: microbiological contamination (*Salmonella*, enterobacteriaceae, total yeasts and filamentous fungi), and, depending on the fermentation media and excipients, mycotoxins,[12] heavy metals (Pb, Hg, Cd) and arsenic. The extent to which spent growth medium is incorporated into the final product should also be indicated. For fermentation products produced by genetically modified microorganisms, identification and quantification of recombinant DNA in the final product should be provided.

– For products produced by chemical synthesis: all chemicals used in the process and any intermediate products remaining in the final product should be identified and quantified.

– For smoke flavourings: polycyclic aromatic hydrocarbons should be identified and where appropriate, quantified.

[11] The selection of mycotoxins and pesticides for analysis should be made according to the different matrices, where appropriate. Residues specified under the undesirable substances directive (Directive 2002/32/EC) and any other pesticide residues of potential concern to target animals and/or consumer safety.

[12] The selection of mycotoxins for analysis should be made according to the different matrices, where appropriate.

2.1.5 Physical state of each form of the product

EFSA recommends the provision of dusting potential (triplicate analysis) for solid preparations representative of the form(s) likely to be marketed to allow an assessment of respiratory exposure for users. Depending on the outcome of these studies and the nature of the substance, further investigations (e.g., particle size distribution in dust) may become necessary.

For liquid preparations, data on vapour pressure, specific weight and where the additive is intended to be used in water, solubility or dispersability should be provided.

The same data should be provided for feed additives already authorised as food additives for which a detailed assessment of user safety was not performed.

2.2 Characterisation of the active substance(s)

2.2.1 Description

A qualitative description of the active substance(s) should be given. This should include purity and origin of the substance(s), plus any other relevant characteristics. Data to establish the identity of the active substance(s) should be provided (e.g., by mass spectrometry, nuclear magnetic resonance).

For natural products, identification tests should be specific for the preparation, and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time, for example, is not regarded as being sufficiently specific. A combination of techniques for the separation and structural analysis is considered suitable (e.g., HPLC/MS^n, GC/MS^n[13]).

An overview of the natural occurrence of the active substance(s) in materials used as feed/food should be provided.

2.2.1.1 Chemical substances

Natural or corresponding synthetic chemically defined flavourings should be described by generic name, chemical name according to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, other commonly used generic names and abbreviations, the FLAVIS number in connection with relevant chemical group and/or Chemical Abstract Service (CAS) Number. The structural and molecular formula and molecular weight must be included. Where relevant, data on isomeric forms (e.g., geometrical or optical isomers) and accompanying structurally related compounds should be included.

For artificial substances, the same requirements apply, where appropriate.

For natural products - botanically defined, the characterisation should include the scientific name of the plant of origin, its botanical classification (family, genus, species, if appropriate subspecies and variety) and the common names and synonyms in official European languages. Synonyms in other language(s) should be given only if relevant to the place of origin. The parts of the plant used (leaves, flowers, seeds, fruits, tubers, etc) should be indicated. The place of cultivation of the plant, the identification criteria and other relevant aspects of the plants should be indicated. Specifications of the applicant for any plant material supplied by a third party should also be provided. For complex mixtures of many compounds obtained by an extraction process, it is recommended to follow the relevant terminology such as essential oil, absolute, tincture, extract and related terms[14] widely used for botanically defined flavouring products to describe the extraction process. *The major components shall be identified and quantified and their range or variability provided.* The phytochemical marker(s) characteristic of the plant of origin must be included. *Special attention shall be given to impurities as*

[13] n: indicates multiple mass spectrometry systems.
[14] Defined in Appendix 4 of the Council of Europe's Report no. 1 on "Natural sources of flavourings", Volume I, Strasbourg, 2000.

mentioned in subsection 2.1.4. The concentrations of substances of toxicological concern for humans or animals which may occur in the plant from which the extract is produced shall also be reported.

For natural products of non-plant origin, an equivalent approach to the above may be used.

The microbial origin (bacteria, yeasts, filamentous fungi and micro-algae) of flavourings produced by fermentation/cultivation should be described and any history of modification of the production organism should be indicated. It should be clearly stated whether the microorganism is genetically modified or not within the meaning of the legislation (Directive 2001/18/EC). The name and taxonomic classification of each microorganism should be provided, according to the latest published information in the International Codes of Nomenclature. Microbial strains should be deposited in an internationally recognised culture collection (preferably in the European Union) and maintained by the culture collection for the authorised life of the additive. A certificate of deposition from the collection, which should specify the accession number under which the strain is held, must be provided.

2.2.2 Relevant properties

Description of physical and chemical properties shall be given. These include, where appropriate, dissociation constant, pKa, electrostatic properties, melting point, boiling point, density, vapour pressure, inflammability, autoignition temperature, explosivity, solubility in water and in organic solvents, K_{ow} and K_d/K_{oc} and any other relevant physical properties. These may be in the form of the material safety data sheet.

Microorganisms used as a production strain should not be capable of producing antibiotic substances that are relevant to antibiotics in human and veterinary medicine. Strains of microorganisms belonging to a taxonomic group that includes members known to be capable of producing toxins or other virulence factors should be subject to appropriate tests to demonstrate at a molecular and, if necessary, cellular level the absence of any cause for concern. technical guidance on the assessment of the toxigenic potential of *Bacillus* species used in animal nutrition.

2.3 Manufacturing process, including any specific processing procedures

To define the critical points of the process that may have an influence on the purity of the active substance or additive a detailed description of the manufacturing process (e.g., chemical synthesis, fermentation, cultivation, hydrolysis, extraction from organic material or distillation and downstream purification steps, including specifications/material safety data sheets for the chemicals used) should be given. The composition of the fermentation/cultivation media should be provided. For genetically modified microorganisms used as source of additives and grown under contained conditions, Directive 90/219/EC applies.

A material safety data sheet for the active substance/additive (see 2.5.2.1) must be provided. Any additional specifications applied to the active substance/additive must also be submitted. The solvents used must be specified. The current maximum levels set for residual solvents used in veterinary drugs (VICH guidance GL18) should not be exceeded.

2.4 Physical-chemical and technological properties of the additive

2.4.1 Stability

Stability is generally measured by the analytical follow-up of the active substance(s) or by persistence of sensory property. For natural products (and some artificial substances) stability may be assessed by monitoring the concentration of one or more appropriate marker substances. Data should include observations at the beginning and end of the storage period.

Where there is a loss of stability, potential degradation or decomposition products should be characterised, where appropriate.

2.4.1.1 Shelf-life of the additive

The expected shelf-life of the additive as marketed should be proposed, based on data from studies performed under the recommended storage conditions, which should be specified. Data should be provided from at least three batches of the additive.

If the shelf-life is already established for an additive authorised for use in food, the relevant studies should be summarised. No additional studies would be required.

2.4.1.2 Stability of the additive used in premixtures and feedingstuffs

The proposal of the applicant for the stability of the additive in premixtures should be supported by data. In this case, the premixtures could consist only of a blend of different flavouring compounds (flavouring premixture). The quantitative and qualitative composition of the premixtures used for the studies should be given. Stability studies in premixtures should be of at least six months' duration.

Stability studies in feedingstuffs are not required for flavourings intended to impart smell to feedingstuffs.

For those substances intended to improve palatability of feedingstuffs, the stability of the additive normally should be studied in feedingstuffs manufactured and stored under common conditions, and if relevant, in premixtures. The quantitative and qualitative composition of the feedingstuffs used for the studies should be given. Stability studies in feedingstuffs should be of at least three months' duration, respectively.

2.4.1.3 Stability of the additive used in water

The stability of the additive intended to be distributed via water for drinking should be studied under conditions simulating practical use (e.g., environment and water temperature, time) for a minimum duration of 48 h. These data should also take into consideration the presence of excipients that could trigger growth of contaminant micro-organisms.

2.4.2 Homogeneity

Homogeneity studies are not required for flavouring compounds.

2.4.4 Physico-chemical incompatibilities in feed

Physico-chemical incompatibilities or interactions that could be expected in feed with feed materials, carriers, other approved additives or medicinal products must be documented.

2.5 Conditions of use of the additive

2.5.1 Proposed mode of use in animal nutrition

The proposed use in feed or water should be defined. The animal species or categories, age group or production stage of animals should be indicated, as appropriate, in accordance with the categories listed in Annex IV of Regulation (EC) No 429/2008. Possible contra-indications should be mentioned.

Details of the proposed method of administration, the proposed dose (minimum and maximum) in the complete feedingstuff, and the proposed duration of administration must be provided. If a particular use in complementary feedingstuffs for some animal species or categories is intended, the (daily) dose should be proposed and justified.

2.5.2 Information related to users/workers safety

2.5.2.1 Chemical substances

A material safety data sheet formatted in accordance with the requirements of Commission Directive 91/155/EEC[15] of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of

[15] Repealed by Regulation (EC) No 1907/2006.

Article 10 of Directive 88/379/EEC as amended by Directive 2001/58/EC must be provided. If necessary, measures for the prevention of occupational risks and means of protection during manufacture, handling, use and disposal shall be proposed.

2.5.2.3 Labelling requirements

Without prejudice to the labelling and packaging provisions laid down in Article 16 of Regulation (EC) No 1831/2003, any specific labelling requirements and, where appropriate, specific conditions for use and handling (including known incompatibilities and contraindications) and instructions for proper use shall be indicated.

2.6 Methods of analysis and reference samples

Details of the requirements are specified in Regulation (EC) No 429/2008. These methods will be evaluated by the European Union Reference Laboratory (EURL). Applicants should refer to Regulation (EC) No 378/2005[16] and the guidance provided by the EURL.

If residues of concern are identified/recognised, methods for their analysis in the relevant tissues/products will be required (e.g., the active substance, its metabolites, the proposed marker substance or any other substance of toxicological concern contained in the additive).

Methods to determine the identity and the characteristics of the additive (composition of the additive, impurities, physical and chemical properties) should be internationally recognised or otherwise fully described.

3. SECTION III: STUDIES CONCERNING THE SAFETY OF THE ADDITIVE

The studies included in this section are intended to permit assessment of:

- *the safety of use of the additive in the target species;*
- *any risk associated with the selection and/or transfer of resistance to antimicrobials and increased persistence and shedding of enteropathogens;*
- *the risks to the consumer of food derived from animals given feedingstuffs containing or treated with the additive or which could result from the consumption of food containing residues of the additive or its metabolites;*
- *the risks from respiratory, other mucosal tissue, eye or cutaneous contact for persons likely to handle the additive as such or as incorporated into premixtures or feedingstuffs; and*
- *the risks of adverse effects on the environment, from the additive itself, or products derived from the additive, either directly and/or excreted by animals.*

Where the additive has already been assessed for safety for food use by a European scientific body, a copy of the most recent safety assessment should be provided. This should be supplemented with any relevant data subsequently produced. Reference to any assessments made by other bodies (e.g., JECFA) should be included in the dossier.

All assessments of safety must be based on the highest proposed use level in animal nutrition.

The safety of natural products may be assessed on the basis of major and characteristic components and also considering minor substances of toxicological concern. Applicants are advised to refer to the "EFSA Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern". Alternatively, the natural product as such may be assessed. If the major or characteristic components are not already authorised as chemically defined flavourings or as feed additives, then it has to be verified whether they are substances of toxicological concern for humans or animals, and their

[16] Last amended by Regulation (EC) No 885/2009. OJ L 254, 26.9.2009, p. 58.

toxicological properties have to be provided. Use of the source material as a recognised food or feedstuff would be taken into consideration.

3.1 Studies concerning the safety of use of the additive for the target species

Any known pharmacological or related properties should be reported for natural or corresponding chemically defined flavourings and reference made to relevant scientific literature (preferably from peer-reviewed journals).

3.1.1 Tolerance for the target species

The aim of the tolerance test is to provide a limited evaluation of short-term toxicity of the additive to the target animals. It is also used to establish a margin of safety, if the additive is consumed at higher doses than recommended.

All studies reported in this section must be based on the additive described in Section II.

For flavourings already authorised for use in food, the safety for target species may be assessed by a comparison between the level of intake by the target species from feed and that by humans from food.[17] Any metabolism and toxicological data on which the assessment for human use was made shall be submitted.

If the use level in the target animals [expressed as quantity per metabolic body weight (usually $mg/kg^{0.75}$)] is similar to that in humans (or less), a tolerance study is normally not required. The figures for body weight and feed intake to be used for the different categories of major species are given in Table 1.

Table 1: Body weight and feed intake of major species

Animal category	Body weight (kg)	Metabolic body weight ($kg^{0.75}$)	Mean feed intake (g/day)
Chickens for fattening	2	1.7	120
Turkeys for fattening	12	6.4	400
Laying hens	2	1.7	120
Piglets	20	9.5	1000
Pigs for fattening	100	31.6	3000
Sows	200	53.2	6000
Veal calves (milk replacer)	100	31.6	2000
Cattle for fattening	400	89.4	8000
Dairy Cows	650	128.7	20000
Salmonids	2	1.7	40

Mean values for dogs are not tabulated due to the high variation in adult body weight. For cats, a body weight of 3 kg should be considered. For the purpose of intake comparison, feed consumption of 2% of the respective body weight could be taken.

Where the proposed level of intake of the target animal is higher than that of humans, or when the compound is not authorised for use in food, the safety for target species may be assessed taking into account:

[17] Until guidance on the calculation of human exposure to food flavourings is made available by EFSA, applicants are advised to make use of the Single Portion Exposure Technique (SPET) used by JECFA (Sixty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. Summary and conclusions. Geneva, 17-26 June 2008).

- the thresholds of toxicological concern (TTC),[18] according to the Cramer structural class to which the compound was assigned. If the intended maximum feed concentration of a flavouring compound in feed for target species is below the concentration indicated in Table 2 according to its Cramer class, no tolerance studies are required. The "maximum acceptable feed concentrations" in Table 2 are derived from the thresholds of the TTC approach, including a safety factor of 100, and based on approximate body weight and feed intake of animal categories.

Table 2: Maximum acceptable feed concentrations of flavouring compounds according to their Cramer classes

	Maximum acceptable feed concentration by Cramer structural class (mg/kg)		
	Class III	**Class II**	**Class I**
Major species (all categories)			
Poultry	0.05	0.30	1.00
Pigs	0.05	0.30	1.00
Cattle	0.08	0.50	1.50
Salmonids	0.08	0.50	1.50
Non food-producing animals	0.08	0.50	1.50

or

- the feed concentration derived from the lowest NOAEL (or by benchmark dose procedure) of appropriate substance-specific toxicological studies,[19] applying a safety factor of 100. The conclusions obtained for an individual flavouring may be extended to other flavourings belonging to the same structural group (e.g., an FGE).

Tolerance studies are needed when the safety of the proposed dose for the target species cannot be established from the procedures described above.

For natural products (extracts), for which no substances of recognised toxicological concern are identified, the same procedure as described above should be followed for each major component. Alternatively, the safety of a whole extract could be assessed based on specific toxicological studies (see above) or directly investigated in a tolerance study.

When needed, tolerance studies should be performed in the relevant target species/categories of animals. If the application is for all animal species, tolerance studies are required in only three major target species (a monogastric, a ruminant, poultry or a salmonid) provided that they show a comparable and wide margin of safety (at least ten). The conclusions obtained for an individual flavouring may be extended to other flavourings belonging to the same structural group (e.g., an FGE).

For details on how to perform and report tolerance studies, see the technical guidance on tolerance and efficacy studies in target animals.

3.1.2 Microbial studies

Microbiological studies may be required when:

- the additive is or contains a substance known or demonstrated to have a significant antimicrobial effect at feed concentration.
- a tolerance test gives an indication of adverse effect possibly related to intestinal disorders.

[18] JECFA (FAO/WHO, 1996, Food additive series 35, IPCS, WHO Geneva); Barlow, S. 2005. Threshold of toxicological Concern (TTC). A tool for assessing substances of unknown toxicity present at low levels in the diet. ILSI Europe Concise Monograph Series.

[19] These should include at least a 90 day oral toxicity study.

For the details on how to perform microbial studies, see the technical guidance on microbial studies

3.2 Studies concerning the safety of use of the additive for the consumer

The aim is to evaluate the safety of the additive for the consumer and to establish potential residues of the additive or its metabolites in food derived from animals given feed or water containing or treated with the additive. This section consists of metabolic and residue studies (3.2.1.), toxicological (*in vitro* and *in vivo*) studies (3.2.2) and the assessment of consumer safety (3.2.3).

Studies concerning safety for consumers are not required for additives intended to be used in non-food producing animals only.

If the use of the flavouring compound as feed additive is not expected to lead to the exposure of the consumer to a different qualitative pattern of metabolites than when used in food (evidence can be provided by literature, database search, etc.), the following applies:

Assessment of consumer safety is not necessary for:

- flavouring compounds already authorised for use in food for which an acceptable daily intake (ADI) is not specified.[20]
- extracts in which the major components fall in the category above, and no substances of toxicological concern are identified.
- flavouring compounds or extracts already authorised as additives for a food-producing species at a similar or higher use level.

Residue data in food of animal origin and an estimation of total consumer exposure (direct intake[21] plus that resulting from use of the flavouring compound in animal feed) are required for:

- flavourings already authorised for the use in food with an established ADI (or some other indicator of maximum intake).
- natural products (extracts) in which one or more of the major components have an established ADI (or some other indicator of maximum intake), and no substances of toxicological concern are identified.

An estimation of total consumer exposure (direct intake plus that resulting from use of the flavouring compound in animal feed) should be provided for:

- flavouring compounds authorised for use in food following the TTC approach.
- natural products (extracts) in which the major components have been assessed following the TTC approach, and no substances of toxicological concern are identified.

If the use of the additive in feed is likely to result in a consumer exposure exceeding the threshold applied, further toxicological studies would be required.

If the pattern of metabolites is (expected to be) qualitatively different when used in feed than when used in food, further toxicological/residue data may be required.

Full section 3.2 applies (i.e., a complete set of metabolism, residue and toxicology data) for:

[20] Without an explicit indication of the upper limit of intake, assigned to substances of very low toxicity, following an evaluation by a European or international body.

[21] Until guidance on the calculation of human exposure to food flavourings is made available by EFSA, applicants are advised to make use of the Single Portion Exposure Technique (SPET) used by JECFA (Sixty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. Summary and conclusions. Geneva, 17-26 June 2008).

- flavouring compounds not authorised for use in food
- natural products (extracts) in which one or more major components have not been assessed for safety

unless they can be assigned to a FGE previously assessed, in which case the TTC approach can be applied.

In the case of natural products (extracts), tests may be done for the individual components or alternatively for the whole product.

3.2.1 Metabolic and residue studies

The establishment of the metabolic fate of the additive in the target species is a determinant step in the identification and quantification of the residues in the edible tissues or products derived from the animals given the feed or water containing the additive.

The purpose of metabolic studies is to evaluate the absorption, distribution, biotransformation and excretion of the additive in the target species and in a laboratory animal, if necessary.

The requirement for residue studies is limited to a comparison of residue levels in tissues and products from an untreated group to the group administered the highest dose of the additive proposed without a withdrawal time.

3.2.2 Toxicological studies

The safety of the additive for the consumer is typically assessed on the basis of the toxicological studies performed in vitro and in vivo on laboratory animals.

If toxicological studies are required, *in vitro* genotoxicity/mutagenicity studies and a subchronic (90 day) oral toxicity study should be provided. For artificial flavourings, which are considered as xenobiotics, a complete set of toxicological studies is normally required.

For details on how to assess consumer safety, refer to the technical guidance on consumer safety.

3.3 Studies concerning the safety of use of the additive for users/workers

Workers can be exposed mainly by inhalation or topical exposure while manufacturing or handling or using the additive.

User safety is established on the basis of a final formulation. However, once an active substance has been authorised as a sensory additive, different formulations can be placed on the market with reference to that authorisation. Consequently, not all forms of the product can be directly tested for user safety. For assessing the safety for the user of sensory additives, the active substance is the principal concern provided that other components do not introduce safety issues.

Therefore, assessment of user safety will be based on the available specific studies, the MSDS, and the nature of the active substance(s).

Additives with a high dusting potential or those used under circumstances which could generate aerosols are of particular concern. Any data on dusting potential will be used for exposure assessment.

Information on precautionary measures to be taken when handling the additive should be provided (see 2.5.2). *However, use of personal protective devices should only be regarded as a measure of last resort to protect against any residual risk once control measures are in place. It is preferable, for example, to consider reformulation of the product.*

For details on how to assess user/worker safety, refer to the technical guidance on user safety.

3.4 Studies concerning the safety of use of the additive for the environment

Administration of additives typically occurs over long periods, often involves large groups of animals and the active substance(s) may be excreted to a considerable extent either as the parent compound or its metabolites.

To determine the environmental impact of additives, a stepwise approach should be followed. All additives have to be assessed through Phase I to identify those additives which do not need further testing. For the other additives a second phase (Phase II) assessment is needed to provide additional information, based upon which further studies may be considered necessary.

The impact on the environment as a result of the Phase I assessment will be considered negligible if:

- the substance is a physiological/natural substance whose use will not result in a substantial increase in concentration in the environment; or
- the additive is intended for non food-producing animals only.

For additives produced by genetically modified microorganisms the specific requirements of the "Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use" should be satisfied.

For details on how to assess environmental safety, refer to the technical guidance on environmental risk assessment.

4. SECTION IV: STUDIES CONCERNING THE EFFICACY OF THE ADDITIVE

In general, studies should demonstrate the efficacy for each proposed use under the recommended conditions of use. Such studies must permit the evaluation of the efficacy of the additive according to common farming practices in the EU.

Flavourings intended to influence feed smell

For flavourings already authorised for use in food, where the functions of the additive applied for feed use and described for food use are similar, no further demonstration of efficacy is generally necessary.

For flavourings not authorised for use in food, efficacy may be demonstrated by submission of studies, peer-reviewed publications (preferably recent) and/or material other than studies.

Flavourings intended to increase feed palatability

Evidence of increased feed palatability should be demonstrated by means of animal studies in the appropriate target species. If the application is for all animal species, then at least studies should be provided for a ruminant and a monogastric mammals and a poultry species.

For details on how to perform and report efficacy studies, see the technical guidance on tolerance and efficacy studies in target animals.

4.6 Studies on the quality of animal products

Evidence should be given that the additive does not have an effect on the sensory/technological characteristics of food deriving from animals fed the treated feed.

Evidence can be given by reference to scientific literature or experience from practical use. If specific studies are performed, food products from an unsupplemented group should be compared with equivalent products from a group receiving the highest dosage proposed for the additive. The data should allow statistical evaluation.

5. SECTION V: POST-MARKET MONITORING PLAN

A post-market monitoring plan is required only for sensory additives that are products consisting of, containing or produced from GMOs, in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effects resulting from the use of the additive on human or animal health or the environment, in accordance with the characteristics of the products concerned.

The design of the monitoring plan shall be detailed on a case-by-case basis and identify who (e.g., applicant, users) will carry out the various tasks that the monitoring plan requires, who is responsible for ensuring that the monitoring plan is set into place and carried out appropriately. The post-market monitoring plan should in all cases ensure that there is a route by which the competent control authorities, the Commission and the EFSA are informed of any observed adverse effects.