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SCIENTIFIC OPINION

Guidance for the preparation of dossiers for nutritional 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 nutritional additive is any substance added to feed to satisfy the nutritional needs of animals.

The category 'nutritional additives' is further grouped into four functional groups (Annex I of Regulation (EC) No 1831/2003):

(a) vitamins, pro-vitamins and chemically well-defined substances having similar effect;

(b) compounds of trace elements;

(c) amino acids, their salts and analogues;

(d) urea and its derivatives.

[1] On request from EFSA, Question No EFSA-Q-2010-01158, 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 nutritional additives, adopted in July 2008 (EFSA-Q-2008-403). The following sections have been updated: 2, 3.2, 3.3 and 4

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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 the 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 shall 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[4] 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 shall be encouraged. Such methods shall 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 as laid down in Directive 2004/10/EC and/or EN ISO/IEC 17025:2005. 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, a post-market monitoring proposal and a labelling proposal as referred to in Article 7(3) of Regulation (EC) No 1831/2003.

[4] OJ L 276, 20.10.2010, p. 33.

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 shall 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 shall 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

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.

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 nutritional 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 nutritional 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 nutritional additives there is no distinction between the active substance and the additive.

2.1.1 Name of the additive

The name of the additive (characterisation of the active substance(s) or agent(s) as defined in the subsections 2.2.1.1 and 2.2.1.2) should be given.

2.1.2 Proposal for classification

A proposal for the classification of an additive for one or more categories[5] *and functional groups according to its main functions under Article 6 and Annex I of Regulation (EC) No 1831/2003 shall 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 or agents also should be provided.

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

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

The active substance(s)/agent(s) and all other components of the additive shall 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 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 the 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 should 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 products: microbiological contamination (*Salmonella*, enterobacteriaceae, total yeasts and filamentous fungi), and, depending on the fermentation media and excipients, mycotoxins,[6] 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 plant derived substances: microbiological and botanical contamination (e.g. castor oil plant, weed seeds, rye ergot in particular), mycotoxins, dioxins and dioxin-like PCBs,

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

pesticides, [7] and, where appropriate, substances of toxicological concern known to occur in the original plant;

- for animal derived substances: microbiological contamination, heavy metals and arsenic, where appropriate;
- for compounds of trace elements: 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 shall 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 shall be given. This shall include purity and origin of the substance or agent, plus any other relevant characteristics.

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 of chemical substances produced by fermentation shall be described and any history of modification shall 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 micro-organism shall be 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.*

[7] 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.

For Genetically Modified Microorganisms (GMM) the description of the genetic modifications shall be given. Applicants are requested to provide data in accordance with Section III (Information requested in applications for GMMs and/or their products) of the "Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use". *The unique identifier for each GMO, as referred in Commission Regulation (EC) No 65/2004 of 14 January 2004 establishing a system for the development and assignment of unique identifiers for genetically modified organisms, must be included.*

2.2.2 Relevant properties

2.2.2.1 Chemical substances

Description of physical and chemical properties shall 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 shall 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 (see technical guidance on microbial studies).

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. 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/agent(s) 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 shall be provided.*

For GMMs used as source of additives and grown under contained conditions, Directive 90/219/EC applies. A description of fermentation processes (culture medium, fermentation condition and downstream processing of the fermentation products) shall be included.

2.3.2 Additive

A detailed description of the manufacturing process of the additive shall be submitted. The key stages in the preparation of the additive including the point(s) of introduction of the active substance(s)/agent(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. 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.

For compounds of trace elements (including chelates) stability studies are generally not required. If specific effects are indicated or claimed for a particular form of the trace element (e.g., organometallic compounds, nanoparticles) the stability of that specific form of the additive should be followed.

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[8] as a substitute for analytical data from subsamples will not be considered.

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

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.

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 shall be indicated in accordance with the categories listed in Annex IV of Regulation (EC) No 429/2008. Possible contra-indications shall be mentioned.*

Details of the proposed method of administration and level of inclusion must be provided for premixtures, feedingstuffs or drinking water. In addition, the proposed dose in the complete feedingstuffs and the proposed duration of administration and proposed withdrawal period, if any, 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 for which a maximum legal content exists, there is no need to propose a level of inclusion in premixtures and feedingstuffs, since the level of inclusion will depend on the difference between background and the maximum content.

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[9] 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.

2.5.2.2 Microorganisms

A classification according to Directive 2000/54/EC shall be submitted. For microorganisms not classified in group 1 in this Directive,[10] information shall be provided to customers to allow them to take the relevant protection measures for their workers, as defined in Article 3 (2) of the said Directive.

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,

[9] Repealed by Regulation (EC) No 1907/2006.
[10] In practice, in the absence of any entries under group 1, this information would be required for all micro-organisms.

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/agent 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 CRL**.**

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 an additive has multiple active components, each should be separately assessed for safety for consumers and then consideration given to additivity (exclusion of interactions). Alternatively, when the components of a mixture cannot be fully separated (e.g., a plant extract), 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 studies 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.

Tolerance studies are not required[11] for:

- urea
- amino acids naturally occurring in proteins of plants and animals (and their salts).
- amino acid analogues already authorised as feed additives.
- compounds of trace elements already authorised as feed additives.

[11] Without prejudice of Regulation (EC) No 429/2008.

- vitamins, pro-vitamins and chemically well-defined substances having similar effect which do not have a potential to accumulate.
- vitamins, pro-vitamins and chemically well-defined substances having similar effect which do have a potential to accumulate if their potency is not higher than that of the corresponding vitamin(s).
- nutritional additives produced by fermentation when the production organism is considered by EFSA to qualify for the QPS approach to safety assessment.
- nutritional additives produced by fermentation when the active substance is separated from the crude fermentation product and highly purified (as a guide > 95% of active substance and <1% of unidentified material, on a dry matter basis).

Tolerance studies are required for:

- urea derivatives
- amino acid analogues not already authorised
- compounds of trace elements not already authorised
- novel authorisations of compounds of trace elements
- vitamins, pro-vitamins and chemically well-defined substances having similar effect with a potential to accumulate for which their potency is expected/demonstrated to be higher than that of the corresponding vitamin(s). In that case, elements of the tolerance test (design or criteria) could be followed in one of the efficacy trials.
- nutritional additives produced by fermentation not exempted above.

Where the application is for all animal species/categories tolerance data may be limited to one study in one target species or laboratory animal (the most sensitive in each case).

For additives only intended to be used in **pets and other non food-producing animals,** refer to the guidance for pets and other non food-producing animals.

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

3.1.2. Microbial studies

Microbial studies are generally not required except for compounds of trace elements which have an antimicrobial effect at feed use level. In which case, 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).

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

For **additives already authorised in food**, refer to the specific guidance for additives already authorised for use in food.

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.

Metabolic studies are normally not required. For urea derivatives, ruminal metabolism should be studied.

Residue or deposition studies are only required for:

a) 'vitamins, pro-vitamins and chemically well-defined substances, having similar effect' that have a potential for accumulation in the body.

b) 'compounds of trace elements' where the bioavailability of the element has been enhanced.

c) novel authorisations of compounds trace elements.

In these cases, the technical guidance on consumer safety does not fully apply. For a) and b) the requirement is limited to the comparison of the levels in the relevant tissues or products between two groups, one fed a diet supplemented with the additive applied for and the second a diet containing a reference compound. The dose levels should be selected to deliver the maximum authorised level of the trace element or vitamin when this exists, or the maximum recommended dose of the additive. In occasional cases it may be necessary to define in which form (e.g., chelate) the nutritionally active part of the additive is distributed and deposited in the tissue/products. For c), where a reference compound is not available, at least three dietary supplementation levels of the trace element (including zero, the highest level recommended and an intermediate dose) should be compared.

3.2.2 Toxicological studies

The safety of the additive 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, with the exception of compounds of trace elements. If the active substance is present in a fermentation product, the fermentation product should be tested. The fermentation product tested must be identical to that to be used in the commercial product.

Toxicological studies are required for additives produced by fermentation and, on a case by case basis, for additives not already authorised.

For additives produced by fermentation, *in vitro* genotoxicity/mutagenicity studies and a subchronic (90 day) oral toxicity study must be provided unless:

- the production organism is considered by EFSA to qualify for the QPS approach to safety assessment; or .
- the active substance is separated from the crude fermentation product and highly purified (as a guide <1% of unidentified material and > 95% of active substance, on a dry matter basis).

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

For other additives not already authorised, the need for toxicological studies should be judged on a case by case basis, taking into account the nature of the compound and the level and nature of exposure.

3.2.3 Assessment of consumer safety

Assessment of consumer safety is not required for amino acids.

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/agent has been authorised as a nutritional 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 nutritional additives, the active substance(s)/agents(s) 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)/agent(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 shall 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 shall 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/agent is a physiological/natural substance (e.g., vitamins, amino acids, urea) 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 shall demonstrate the efficacy for each proposed use. Such studies must permit the evaluation of the efficacy of the additive according to common farming practices in the EU.

Efficacy studies are not required for:

- urea
- amino acids naturally occurring in proteins of plants and animals
- amino acid salts and analogues already authorised as feed additives
- compounds of trace elements already authorised as feed additives
- vitamins, pro-vitamins and chemically well-defined substances having similar effect already authorised as feed additives

A short-term study is required to support efficacy for:

- urea derivatives
- amino acid salts and analogues not already authorised as feed additives
- compounds of trace elements not already authorised as feed additives
- vitamins, pro-vitamins and chemically well-defined substances having similar effect not already authorised as feed additives

For other (novel) substances for which a nutritional effect is described at least one long term efficacy study should be provided.

Generally, it will be sufficient to demonstrate efficacy in a single animal species or category including laboratory animals. The target species should be used for additives specifically designed to be effective in a particular animal species/category (e.g., protected amino acids for ruminants).

Oral administration routes of additives, via feed or water, are principally considered as bioequivalent. Thus there is no preference for the route of administration of the additive.

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 where this is not the effect claimed

These studies are normally not required for nutritional additives. However, in the case of novel authorisations or in the case of substances for which deposition studies are required some considerations should be given to potential sensory and nutritional (and if appropriate, hygienic and technological) effects on food deriving from animals fed with the additive. Rarely, specific studies may be necessary. In such cases, an unsupplemented group should be compared with a group receiving the highest dosage proposed for the additive. *The data shall allow statistical evaluation.*

5. SECTION V: POST-MARKET MONITORING PLAN

A post-market monitoring plan is required 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.

It would generally be sufficient to follow the requirements of the Feed Hygiene Regulation (Regulation (EC) No 183/2005) and Good Manufacturing Practices. The post-market monitoring plan shall 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.