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# Draft guidance on the preparation and presentation of an application for authorisation of a Novel Food

## EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

## Abstract

Following the adoption of a new Regulation ((EU) 2015/2283) of the European Parliament and of the Council on Novel Foods, the European Commission requested the European Food Safety Authority to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of Novel Foods. This opinion provides guidance on the data needed to carry out the safety assessments of Novel Foods and their presentation in a structured format. Minimum requirements which should be covered in all applications relate to the description of the Novel Food, production process, compositional data, specification, proposed uses and use levels, and anticipated intake of the Novel Food. Further sections on the history of use of the Novel Food and/or its source, absorption, distribution, metabolism, excretion, nutritional information, toxicological information and allergenicity should be considered by the applicant by default. If not covered in the application, this should be justified. The application should be comprehensive and complete. Uncertainties should be addressed, and a critical appraisal on data both in favour and not in favour of the safety of the Novel Food should be provided. On the basis of the information provided, EFSA will assess the safety of the Novel Food under the proposed conditions of use.



**Keywords:** guidance, Novel Food, application

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## Summary

Following the adoption of a new Regulation (EU) 2015/2283 of the European Parliament and of the Council on Novel Foods, the European Commission requested the European Food Safety Authority to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of Novel Foods.

This opinion provides guidance on the data needed to carry out the safety assessments of Novel Foods and their presentation in a structured format. Minimum requirements which should be covered in all applications relate to the description of the Novel Food, production process, compositional data, specification, proposed uses and use levels, and anticipated intake of the Novel Food. Further sections on the history of use of the Novel Food and/or its source, absorption, distribution, metabolism, excretion, nutritional information, toxicological information and allergenicity should be considered by the applicant by default. If not covered in the application, this should be justified.

The application should be comprehensive and complete. Uncertainties should be addressed, and a critical appraisal of data both in favour and not in favour of the safety of the Novel Food should be provided.

On the basis of the information provided, EFSA will assess the safety of the Novel Food under the proposed conditions of use.

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## Background as provided by the European Commission

On 25 November 2015, the European Parliament and the Council adopted the Regulation of the European Parliament and of the Council on Novel Foods[1].

The Regulation foresees that all applications for the authorisation of Novel Foods shall be submitted to the Commission who may then request a risk assessment from the European Food Safety Authority (EFSA). In assessing the safety of Novel Foods, EFSA shall, where appropriate, consider the following:

(a) whether the Novel Food concerned is as safe as food from a comparable food category already existing on the market within the Union;

(b) whether the composition of the Novel Food and the conditions of its use do not pose a safety risk to human health in the Union;

(c) a Novel Food, which is intended to replace another food, does not differ from that food in such a way that its normal consumption would be nutritionally disadvantageous for the consumer.

The Regulation also introduces a special procedure for safety assessment for traditional foods from third countries, based on a history of safe food use. In this case, a notification for the placing on the market of a traditional food from a third country is sent to the Commission who forwards it to all the Member States and EFSA. A Member State or EFSA may submit reasoned safety objections on the placing on the market of the notified food. In this latter case, the applicant may transform the notification into an application, for which a safety evaluation will be requested from EFSA. In assessing the safety of these types of Novel Foods, EFSA shall, where appropriate, consider the following:

(a) whether the history of safe food use in a third country is substantiated by reliable data submitted by the applicant;

(b) whether the composition of the food and the conditions of its use do not pose a safety risk to human health in the Union;

(c) where the traditional food from the third country is intended to replace another food, whether it does not differ from that food in such a way that its normal consumption would be nutritionally disadvantageous for the consumer.

The Commission shall adopt implementing rules on administrative and scientific requirements for the preparation and the presentation of the applications for Novel Foods, as well as for the notifications and applications for traditional foods from third countries for the scientific assessment, respectively in accordance with Article 13 and Article 20 of the Regulation. These implementing measures need to be complemented with scientific and technical guidance regarding the information that needs to be submitted by the applicants. In this context, the current Commission Recommendation 97/618/EC2, which is in place for the additional safety assessment of the Novel Food applications under the current rules (Regulation (EC) No 258/973), should serve as the basis for updating the guidance on preparation and presentation of applications for Novel Foods

## Terms of Reference as provided by the European Commission

In accordance with Article 29 of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to update and develop scientific and technical guidance for the preparation and presentation of applications for authorisation of novel foods, and to develop scientific and technical guidance for notifications and applications for authorisation of Traditional Foods from third countries.

## Objectives

This guidance presents a common format for the organisation of the information to be presented in order to assist the applicant in the preparation of a well-structured application to demonstrate the

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council on Novel Foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European
[2] OJ L 253, 16.9.1997, p. 1.
[3] OJ L 43, 14.2.1997, p. 1.

safety of the Novel Food. Adherence to this format will also facilitate easy access to information and scientific data in applications to help EFSA to carry out its evaluation and to deliver its scientific advice in an effective and consistent way.

This guidance for applications of Novel Foods is also intended in providing the type and quality of information EFSA needs to conclude whether or not the Novel Food is safe under the proposed conditions of use. The requirements for preparing and presenting a dossier for the notification of a traditional food from third countries are dealt with by a separate Guidance document.

## Scope

The Guidance presented in this document is for preparing and presenting applications for authorisation of a Novel Food under Article 10 of Regulation (EU) 2015/2283.

It should also serve applicants in preparing and presenting an application under Article 16 of Regulation (EU) 2015/2283, if the application concerns data other than those on the "history of safe food use in a third country". For the preparation of a notification dossier on the "history of safe food use in third country" of a traditional food as defined by Article 3 of the Regulation (EU) 2015/2283, the applicant should consider the guidance on the preparation and presentation of the notification for authorisation of traditional foods from third countries (EFSA, 2016).

The Guidance will be kept under review and will be amended and updated as appropriate in the light of experience gained from the evaluation of Novel Food applications.

## Definitions

As per Article 3, paragraph 2 of Regulation (EU) 2015/2283

(a) *'Novel Food'* means any food that was not used for human consumption to a significant degree within the Union before 15 May 1997 irrespective of the dates of accession of Member States to the Union and that falls under at least one of the following categories:

(i) food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997;

(ii) food consisting of, isolated from or produced from microorganisms, fungi or algae;

(iii) food consisting of, isolated from or produced from material of mineral origin;

(iv) food consisting of, isolated from or produced from plants or their parts, except when the food has a history of safe food use within the Union and is consisting of, isolated from or produced from a plant or a variety of the same species obtained by:

– traditional propagating practices which have been used for food production within the Union before 15 May 1997; or

– non-traditional propagating practices which have not been used for food production within the Union before 15 May 1997, where those practices do not give rise to significant changes in the composition or structure of the food affecting its nutritional value, metabolism or level of undesirable substances;

(v) food consisting of, isolated from or produced from animals or their parts, except for animals obtained by traditional breeding practices which have been used for food production within the Union before 15 May 1997 and the food from those animals has a history of safe food use within the Union;

(vi) food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae;

(vii) food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances;

(viii) food consisting of engineered nanomaterials as defined in point (f) of this paragraph;

(ix) vitamins, minerals and other substances used in accordance with Directive 2002/46/EC, Regulation (EC) No 1925/2006 or Regulation (EU) No 609/2013, where:

– a production process not used for food production within the Union before 15 May 1997 has been applied as referred to in point (a) (vii) of this paragraph; or

– they contain or consist of engineered nanomaterials;

(x) food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements as defined in point (a) of Article 2 of Directive 2002/46/EC.

## General Principles

- This document should be read in conjunction with Regulation (EU) 2015/2283 of the European Parliament and of the Council as regards Novel Foods and current and future EU guidelines and Regulations. In addition, several guidances from EFSA are of relevance for the preparation of applications for authorisation of Novel Foods. They are listed throughout the present document. Over time, also new guidances will be developed which may be of relevance for Novel Food applications. The Panel notes that the references to other EFSA Guidances provided in this document is not exhaustive. Other EFSA Guidances, for example those from the EFSA Scientific Committee or the ANS Panel might be applicable in specific cases. Applicants are therefore advised to consult the EFSA webpage and consider the most up-to-date versions of the available and applicable guidances.
- The term "application" hereafter means a stand-alone dossier containing the information and the scientific data submitted for the safety assessment of a Novel Food.
- It is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data (including both data in favour and not in favour) that are pertinent to the safety of the Novel Food. As such, an application to demonstrate the safety of the Novel Food should be comprehensive and complete. The identification of data pertinent to the safety of the Novel Food should be performed and documented in order to demonstrate that the application covers the complete information available on the Novel Food. Where applicable, the published literature should be reviewed by taking into account systematic review principles (EFSA, 2010a). The methods used to identify relevant data, including databases used and the criteria of literature searches should be reported. Full study reports should be provided if available.
- The applicant should provide their considerations at the end of individual sections on how the information supports safety of the Novel Food under the proposed conditions of use. Uncertainties should be addressed, and a critical appraisal on data both in favour and not in favour of the safety of the Novel Food should be provided.
- The structure of the application should follow the sections presented in this Guidance. The information requested on the description of the Novel Food (section 1), production process (section 2), compositional data (section 3), specifications (section 4), and proposed uses and use levels and anticipated intake of the Novel Food (section 6) constitutes the minimum requirements which should be covered in all applications. Further sections on the history of use of the Novel Food and/or its source (section 5), absorption, distribution, metabolism, and excretion (section 7), nutritional information (section 8), toxicological information (section 9) and allergenicity (section 10) should be considered by the applicant by default. If not covered in the application, this should be justified.
- Deviations from the requirements specified in the respective sections described in this Guidance should be justified.
- Analyses/tests should be performed in a competent facility that can certify the data. Quality systems in place for control/documentation should be indicated. Information on the accreditation of involved facilities and certificates of analyses should be provided. Whenever official guidelines (e.g. OECD, EMA and ICH) and quality systems (e.g. GLP, GMP, GCP and applicable ISO systems) were followed, the applicant should indicate compliance.
- In accordance with Directive 2010/63/EU4 on the protection of animals used for experimental and other scientific purposes, and as reiterated in Regulation (EU) 2015/2283, tests on animals should be replaced, reduced or refined. Unnecessary use of animals should be avoided and any studies carried out should be those necessary to demonstrate the safety of the Novel Food.
- The decision on granting the protection of proprietary data under Article 26 of Regulation (EU) 2015/2283 falls under the responsibility of the European Commission. With respect to

[4] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010, p. 33.

the handling, use and protection of proprietary data by EFSA, it should be noted that where an application includes a request for the protection of proprietary data, the NDA Panel considers in its opinion whether the safety of the Novel Food could have been assessed without the data claimed as proprietary by the applicant.

- The decision on confidential treatment of information submitted under Article 23 of Regulation (EU) 2015/2283 falls under the responsibility of the European Commission. As per Article 23(5) of the Regulation, EFSA shall take necessary measures to ensure appropriate confidentiality of the information received under this Regulation, except for information which is required to be made public in order to protect human health. .

# Organisation and content of the notification

The following information should be provided in the application and the structure should follow a common format. Data provided in the application should be organised into **two Parts:**

**Part 1** contains information specific to the Novel Food with respect to description of the Novel Food (section 1), production process (section 2), compositional data (section 3), specifications (section 4), the history of use of the Novel Food and/or its source (section 5), proposed uses and use levels and anticipated intake (section 6), absorption, distribution, metabolism and excretion (section 7), nutritional information (section 8), toxicological information (section 9) and allergenicity (section 10). It includes a list of all references.

**Part 2** comprises the glossary or abbreviations of terms quoted throughout the application, the certificates (on the accreditation of laboratories, certificates of analyses), contains all pertinent scientific data (published and unpublished) including copies/reprints of pertinent publications identified and the full study reports of unpublished, pertinent, scientific opinions of national/international regulatory bodies..

# Structure of Part 1

## Introduction

The nature of the Novel Food should be summarised in an introductory paragraph, including the source, the main aspects of the production process and typical compositional features. Its purpose and intended use should be described.

## 1. Description of the Novel Food

The following information should be provided, depending on the category(ies) under which the Novel Food fall(s):

### 1.1. Chemical substances

- Chemical name, when appropriate, according to IUPAC nomenclature rules
- CAS number (if this has been attributed) and other identification numbers
- Synonyms, trade names, abbreviations
- Molecular and structural formulae; stereochemistry
- Molecular mass (Da)

### 1.2. Polymers

- Structural formulae of monomers and starting materials, reagents involved in the polymerisation
- Structure of the polymer, number average molecular weight, and weight average molecular weight
- Nature and degree of modification of the polymer

- Particle size, shape and distribution

### 1.3. Foods consisting of, isolated from or produced from microorganisms, fungi or algae

- Scientific (Latin) name (family, genus, species, strain)
- Synonyms that may be used interchangeably with the preferred scientific name
- Procedure of identification
- Genetic characterization (molecular typing) for unicellular organisms
- Origin and history of the organism
- Deposition in an officially-recognised culture collection with access number.

### 1.4. Food consisting of, isolated from or produced from material of mineral origin.

This section concerns inorganic mineral constituents isolated from rocks and utilized as inorganic or organic salts or chelates.

- Chemical name according to IUPAC nomenclature rules
- CAS number (if this has been attributed) and other identification numbers
- Synonyms, trade names, abbreviations
- Molecular and structural formulae
- Molecular mass (Da)
- Particle size

### 1.5. Food consisting of, isolated from or produced from plants or their parts[5]

- Scientific (Latin) name (botanical family, genus, species, subspecies, variety with author's name, chemotype, if applicable)
- Synonyms (botanical name) that may be used interchangeably with the preferred scientific name
- Common names (if a trivial or a common name is used extensively, it should be linked to the scientific name and part used)
- Part used (e.g. root, leaf, seed, etc.)
- Geographical origin (continent, country, region)

### 1.6. Food consisting of, isolated from or produced from animals or their parts

- Scientific (Latin) name (zoological family, genus, species, subspecies, breed, if applicable)
- Synonyms that may be used interchangeably with the preferred scientific name
- Common names (if a trivial or a common name is used extensively, it should be linked to the scientific name and part used)
- Part used

[5] These requirements are in line with the EFSA Scientific Committee Guidance on the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. EFSA SC (EFSA Scientific Committee), 2009. Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. EFSA Journal 2009;7(9):1249, 19 pp. doi:10.2093/j.efsa.2009.1249

- Geographical origin (continent, country, region)

### 1.7. Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, fungi or algae

This section concerns cultures of multicellular origin (animals, plants including algae and mushrooms). Foods originating from cultures of other origin should be addressed under 1.3.

- Biological source (taxonomic information on family, genus, species, subspecies, variety)
- Organ and tissue or part of the organism sourced
- Laboratory or culture collection sourced
- Information on the identity of cells
- Cell or tissue substrate used as a Novel Food
- Type of culture

### 1.8. Foods consisting of "engineered nanomaterials"[6]

For Novel Foods containing or consisting of "engineered nanomaterials", the parameters for characterisation and identification of engineered nanomaterials outlined in the EFSA Scientific Committee Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (EFSA SC, 2011a)

## 2. Production process

The process employed to produce the Novel Food (e.g. chemical synthesis, enzyme-catalysis, fermentation or isolation from a natural source) should be described. The description should be detailed enough to allow conclusions to be drawn regarding the impact of the process on the safety and nutritional value of the Novel Food. It should specifically focus on potential by-products, impurities or contaminants that could raise safety concerns.

Information should be provided as to whether the process is novel, i.e. not used for food production within the Union before 15 May 1997, and to characterise the novel aspects of the process.

Information on the raw materials, starting substances, other employed reagents and solvents should be provided. Operational limits and key parameters of the production process should be given. Measures implemented for production control and quality assurance should be described (e.g. HACCP, GMP, ISO). A production flow chart should be provided, including quality control checks.

For example, for Novel Foods obtained via chemical synthesis, the reaction sequence, side reactions and purification steps should be described. Information on reaction conditions (e.g. temperature, duration of the reaction, and catalyst), chemical or physical purification methods (e.g. solvent extraction and crystallisation) should be reported.

For Novel Foods derived from plant, animal or microbiological sources, the applicant should describe in detail the process by which the raw material is converted into a preparation, e.g. extraction or other procedure(s), as well as standardisation procedures. Information should also be provided on the handling of the sources, for example the growth and harvesting conditions for plants and fungi (e.g. wild or cultivated, cultivation practices including the use of pesticides, and time of harvest in relation to both season and stage of the plant growth); the breeding, rearing, feeding and farming conditions for farmed animals or the hunting, catching or collecting and killing of wild living animals; the culture conditions for microbes and microalgae.

For Novel Foods derived from plants, but especially when intended for use as an ingredient for supplements, specific considerations and complementary information is provided in the EFSA Guidance on safety assessment of botanicals and botanical preparations (EFSA, 2009)

[6] As defined in Regulation (EU) 2015/2283

# 3. Compositional data

The information should include qualitative and quantitative data on the composition as well as physico-chemical, biochemical and microbiological properties of the Novel Food.

Section 3.1 outlines general data requirements applicable to all Novel Foods. Sections 3.2 and 3.3 set specific requirements depending on the complexity of the Novel Food, i.e. whether it is a single substance or a simple mixture thereof, a complex mixture or a whole food.

Validated methods should be used for the analyses, preferably nationally or internationally-recognised methods (e.g. Association Of Analytical Communities (AOAC), American Chemical Society (ACS), European Pharmacopoeia (EP)). The respective methods of analysis (with their limit of detection (LOD) and limit of quantification (LOQ) should be described together with their references. Certificates of analyses and information on the accreditation of laboratories should be provided. If in-house methods are employed, they should be fully described, and the results of the respective validation procedures should be provided. If the analyses are not performed in accredited laboratories, justification should be provided.

The analytical information should preferably be provided on at least five representative batches of the Novel Food that have been independently produced (i.e. with independent batches of raw materials). When several production processes are proposed, such data should be provided for each given process. Compositional data and their variability should support the setting of a specification which is representative of the product to be marketed (Section 4).

## 3.1. General requirements

Information on the identities and the quantities of impurities or by-products, residues and chemical and microbiological contaminants should be provided. The type and spectrum of potential target analytes should be considered in the light of the sources and the production process. For example, for substances obtained by chemical synthesis, residual starting materials and by-products anticipated from side-reactions should be analysed; for substances produced via microbial fermentation, the presence of undesirable metabolites should be investigated; for substances isolated via extraction, data on residues of the solvent used should be provided.

## 3.2. Single substances and simple mixtures thereof

For single substances, the following data should be provided:

- Identity tests (e.g. UV-VIS, IR, NMR, GC-MS, LC-MS)
- Physico-chemical properties (e.g. appearance, melting point, boiling point)
- Solubility data in water and other common solvents
- Particle size, shape and distribution
- Minimum purity value

Simple mixtures are mixtures whose components can be fully chemically characterised. For simple mixtures of defined substances, information on the identities and the relative ratios of all components should be provided. This should allow the elaboration of a complete mass balance.

## 3.3. Complex mixtures and whole foods

In complex mixtures (e.g. extracts, protein hydrolysates) or whole foods (e.g. milk, meat, fruits, seeds), all constituents cannot be fully chemically characterised and/or identified.

A qualitative and quantitative characterisation of the main constituents should be performed, at least via sum parameters. For whole foods this should include proximates analyses (i.e. ash, moisture, protein, fat and carbohydrate). On the basis of these data, a mass balance should be set up. The amount of unidentified constituents (calculated as 100 % minus the percentage characterised) should be indicated and should be as low as possible.

For the classes of naturally or chemically derived components which characterise the nature of the Novel Food (e.g. peptides, phospholipids, carotenoids, phenolics, sterols), comprehensive qualitative and quantitative data should be provided.

Qualitative and quantitative data on nutritionally relevant inherent constituents (e.g. micronutrients) should be given.

In addition, qualitative and quantitative data on toxic, addictive, psychotropic or other substances of possible concern to human health, of the Novel Food should be provided. Furthermore special attention should be given to the presence of potential allergens.

Information should also be provided on the identities and the quantities of impurities or by-products, residues and contaminants. The type and the spectrum of potential target analytes should be considered in the light of the sources and the production process (Section 3). For example, for substances produced via microbial fermentation, the presence of undesirable metabolites, such as mycotoxins, has to be investigated. For substances isolated via extraction, residues of the employed solvent should be provided.

### 3.4. Stability

The stability of the Novel Food should be evaluated in order to identify hazards which might arise during storage.

Stability tests should consider constituents and parameters of the Novel Food which may be susceptible to changes during storage and which may affect its safety or serve as indicators for alterations which could have an impact on the safety of the food. The degradation products should be identified.

Depending on the nature and type of the Novel Food, the assessment should consider the physico-chemical, biochemical and microbiological stability of the Novel Food under normal conditions of storage, including the effects of packaging, the storage temperature and the environment (light, oxygen, moisture, relative humidity). Information on the normal storage conditions of the Novel Food, as well as on the storage conditions under which the stability tests were performed, should be provided.

If the Novel Food is used as an ingredient added to other foods, its stability in the processed foods should be investigated (e.g. effect of processing temperature, pH, and other constituents in the processed foods).

## 4. Specifications

The specifications define the key parameters which characterise and substantiate the identity of the Novel Food, as well as the limits for these parameters and for other relevant physico-chemical, biochemical or microbiological parameters. The specifications will be used, among other compositional data, to evaluate whether the data provided to demonstrate the safety are relevant to the Novel Food intended to be placed on the EU market. In addition, the limits set in the specifications for toxicologically and/or nutritionally relevant components will be considered in the risk assessment.

On the basis of the analytical characterisation of the Novel Food (sections 1 and 3), the applicant should propose specifications, in the form of a table.

A rationale for the selected parameters should be provided. As a minimum, the specification should include contents and/or limits for the parameters characterising the identity of the product; the minimal purity; and limits acceptable for impurities and degradation products, in particular those of toxicological or nutritional relevance. In the absence of legal requirements, maximum levels of contaminants (e.g. microorganisms, mycotoxins, heavy metals, pesticide residues, PAHs, dioxins and dioxin-like PCBs) should be included.

The specifications should provide the methods used for the analysis of all parameters.

# 5. History of use of the Novel Food and of its source

## 5.1. History of the source

Data on the composition, production and on the experience from use of products, other than the Novel Food itself, derived from the source may provide relevant aspects for further consideration, for example regarding critical substances contained in the source, potential hazards or precautions. With respect to foods derived from plants, relevant information may be found in EFSA's Compendium on botanicals (EFSA SC, 2012a).

## 5.2. History of use of the Novel Food

Data may be available on the use of the Novel Food as food in countries outside of the EU and on non-food uses. Such data may provide information which could be relevant for assessing the safety of the Novel Food.

Such information could include a description of the extent of use as a food and/or for non-food purposes, the population group for which the food has been a part of their diet, its role in the diet, the handling and preparation of the food and on precautions. A comprehensive literature review of human studies reporting on relevant safety outcomes should be performed.

The applicant should not only consider and limit the literature search to the Novel Food itself, but should also consider searching for studies with specific and typical components of the Novel Food and for studies with similar foods from the same or other closely related sources (e.g. other varieties or subspecies or related species of the same genus or family).

# 6. Proposed uses and use levels and anticipated intake

Estimated intakes of the Novel Food for the European population are needed to evaluate its dietary and nutritional significance and carry out the risk characterisation. Intakes are estimated based on the proposed use levels of the Novel Food and data on actual food consumption.

A rationale for the target population, proposed uses and use levels, precautions and restrictions of use should be provided with cross-referencing to safety relevant data.

Where potential health hazards have been identified on the basis of the composition, toxicological or other data, they should be discussed and adequately addressed in the proposed conditions of use to ensure that the consumption of the Novel Food is safe for the target population.

It is of utmost importance that the information provided in this section is precise, complete, and free of any ambiguity, because the safety of the Novel Food will be assessed at the proposed conditions of use. If information provided in this section conflicts with information related to conditions of use in any other part of the dossier, priority will be given to the information provided in this section.

## 6.1. Target Population

The applicant should specify the intended target population, e.g. adults, the general population or certain defined population sub-groups.

## 6.2. Proposed uses and use levels

The applicant should specify:

- The form of uses (e.g. as whole food, ingredient, food supplement);
- The food categories in which it is proposed to be used;
- Whether the Novel Food is intended to replace another food;
- The proposed maximum amounts in final product(s);
- The proposed average and maximum daily intakes for different age/gender groups as appropriate;

## 6.3. Anticipated intake of the Novel Food

On the basis of the information provided in section 6.1, estimations of anticipated intakes of the Novel Food are required (per kg body weight and in absolute amounts). Estimations of mean and high (at least 95$^{th}$ percentile) anticipated intake are requested for each target population group (including, where relevant vulnerable groups such as children, pregnant and lactating women). The concurrent consumption of all food categories in which a Novel Food ingredient is proposed to be used, including food supplements, should be addressed in the estimations, possibly considering different consumption scenarios. The highest estimated intake (i.e. at least the 95$^{th}$ percentile) among the population groups from a representative database (e.g. EFSA Comprehensive European Food Consumption database or national dietary surveys) is recommended be used as the starting point for the safety evaluation.

The EFSA Food Additive Intake Model (FAIM) tool[7] was developed to support the calculation of chronic exposure to food additives. Exposure assessment of food additives and intake assessment of Novel Food ingredients share common principles. Thus, the FAIM tool may be used by applicants for the intake assessment of Novel Foods used as ingredients. It allows the applicant to estimate the mean and high exposure to food ingredients for different population groups throughout several European countries by means of pre-defined exposure calculation worksheets (Excel template). For the calculation of high percentiles of intake, the model assumes that an individual might be a high-level consumer of one food category only and would be an average consumer of all the remaining food groups. Thus, the FAIM tool adds the highest of the high levels of intake from one food category (calculated for consumers only) to the mean intake values for the remaining categories (calculated for the total population)..

The food categories available in the FAIM tool reflect the regulatory framework of food additives Regulation (EU) 1333/2008.[8] In case additional or more refined food categories are needed, data from the EFSA Comprehensive European Food Consumption Database[9] may be used by the applicant for intake calculations. Summary statistics of chronic food consumption are available on the EFSA website in the form of Excel worksheets. Detailed information on the database and guidance on its use have been published by EFSA (EFSA, 2011). Anticipated intakes for mean and high-level consumers can be calculated for each food category, through the combination of the intended use level in each food category with mean and high chronic consumption values from the database, respectively.

Summary statistics from the EFSA FAIM tool or the EFSA Comprehensive European Food Consumption Database provide valuable screening estimates of intake, which may in many cases bring sufficient information. In cases where more refined estimates are needed, the applicant should consider more detailed assessments, such as intake calculations based on individual data from national food consumption surveys.

The application should document the methodological aspects of the intake assessment; in particular:

- the sources of data used (sources of food consumption data and food composition data);
- the scientific principles and methods applied;
- the assumptions made and their rationale; in particular with respect to the assignment of a food to a particular food category, or with respect to the model used for the calculation of high intake levels.

The applicant should consider and discuss the uncertainties related to the assessment; in particular, sources of under- or over-estimations. To this end, the guidance from the EFSA Scientific Committee related to uncertainties in dietary exposure assessment should be considered (EFSA, 2006).

## 6.4. Combined intake from multiple sources

Other potential sources of intake of the Novel Food should be taken into account [such as natural occurrence in food (e.g. lycopene, beta-glucans)]. In such cases, an estimation of the mean and high current intake of the constituent should be provided, in order to assess the extent of the additional

[7] Available online: http://www.efsa.europa.eu/en/applications/foodingredients/regulationsandguidance
[8] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, as amended. OJ L 354, 31.12.2008, p 16-33.
[9] Available online: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

intake of the constituent resulting from its intended use as a Novel Food, in relation to existing dietary intake.

For the estimation of total intake of the Novel Food, data are requested on the combined intake of the Novel Food from all sources. Combined intake is the sum of:

- mean and high intakes of the Novel Food from its proposed uses and maximum use levels;
- mean and high intakes from natural sources (i.e. from the background diet);
- intake from food fortification and supplements;
- intake from other uses.

Any other potential non-dietary sources (e.g. from consumer products such as cosmetics, and from pharmaceuticals) should also be considered and taken into consideration in the total exposure assessment, where relevant.

### 6.5. Estimate of exposure to undesirable substances

Exposure estimates are also to be provided for relevant undesirable substances identified in the compositional analysis, for example potential secondary plant metabolites, residues, contaminants, or degradation products. These may be present in the Novel Food due to its source or the manufacturing process, as well as due to its use and storage.

The same approach as that used for the intake estimate of the Novel Food should be followed, in order to describe the anticipated exposure for average and high (typically, 95th percentile) consumers to these constituents for the relevant population groups.

### 6.6. Precautions and restrictions of use

When proposing precautions (including directions for its preparation and/or use) and restrictions of use, all available information on safety should be taken into consideration.

The applicant should specify the population (sub)groups (including population groups with certain physiological conditions) which should avoid consumption of the Novel Food and include the rationale.

## 7. Absorption, distribution, metabolism, and excretion (ADME)

Data on toxicokinetics (absorption, distribution, metabolism, and excretion (ADME)) are important in the assessment of both the nutritional and toxicological impact of a Novel Food. Toxicokinetic data are critical for the development of appropriate toxicity testing strategy (section 9) including the selection of appropriate animal models. They also provide important information for the interpretation of study results. Finally, they constitute an important element of the risk assessment to account for differences between experimental animals and humans.

Applicants are advised to consult the data requirements and tiered approach to toxicokinetic testing which are described in section 4.1 on « Toxicokinetics (ADME) » of the EFSA Guidance for food additive evaluations (EFSA ANS Panel, 2012) (Appendix A). The Panel considers that the toxicokinetics of single substances and simple mixtures should normally be tested according to the same principles as those applied to food additives. As a default, absorption of the Novel Food or its breakdown products should be assessed (Tier 1). Demonstration of negligible absorption may provide a scientific justification for not undertaking higher tiered toxicological studies.

For food additives in the form of complex mixtures, the ANS Guidance states that « *conventional metabolism and toxicokinetic studies may not be feasible for all components in the mixture, but should be provided for toxicologically relevant constituents. Toxicologically relevant constituents are generally considered to be the major components and those other components with known or demonstrable biological or toxicological activity, and should be determined on a case-by-case basis with a scientific justification and the rationale for their selection provided* ». Whole foods should be tested like complex mixtures. The design of toxicokinetic studies may be modified based on the particular complex mixture/whole food being tested.

For Novel Foods, ADME assessment should also address nutritionally significant constituents where toxicokinetic data on these constituents are important considerations for the evaluation of the nutritional impact of the Novel Food (section 8).

With respect to Novel Foods consisting of "engineered nanomaterials", applicants should consider the specific requirements and follow the approach as set out in the EFSA Scientific Committee Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (in particular, sections on in vitro digestion studies and ADME studies) (EFSA, 2010b).

# 8. Nutritional information

The applicant should demonstrate that the Novel Food is not nutritionally disadvantageous for consumers at the proposed conditions of use. For this purpose, in the context of this Guidance, the term nutritional information specifically refers to the role that the Novel Food may play in the diet in terms of its contribution to or interaction with nutrient intakes.

Nutritional information on the Novel Food should include details of its nutrient composition taking into account influences of production, storage and further processing, handling and cooking. The content and effect of anti-nutritional factors in the Novel Food (e.g. inhibiting absorption or modifying bioavailability) and other known and suspected interactions with nutrients should also be assessed.

Use levels and estimated intakes for the target population should be taken into account as specified in section 6 ("Proposed uses and use levels and anticipated intake of the Novel Food"). Intakes of relevant substances from the background diet, both nutritional and anti-nutritional, should be considered for establishing mean and high intake scenarios. The resulting estimates should be discussed in the context of available dietary reference values including tolerable upper intake levels ("upper levels"). Intake estimates for potentially anti-nutritional substances should be compared with health-based guidance (e.g. ADI) values, if available. Vulnerable subgroups such as young children, pregnant and lactating women or subjects with particular metabolic or physiological characteristics should be specifically considered on a case-by-case basis. Where a Novel Food is intended to replace another food, or when a novel production process is applied to a food which is a relevant source for nutrients, the applicant should demonstrate that the Novel Food does not differ in a way that it would be nutritionally disadvantageous for the consumer at the proposed conditions of use.

Apart from an evaluation of the compositional data and an appraisal of the relevant literature and databases, in specific cases, data from investigations *in vitro* and/or in animal models and/or human studies may be needed to address the interaction of the Novel Food with the diet and nutrients. The necessity for such studies may arise from information on the source, the composition and the production of the Novel Food, from documented experience on the uses, preparation and/or handling of the Novel Food (e.g. foods which have been consumed in third countries), mechanistic data, outcomes from studies on ADME, and from pharmacodynamic, mechanistic, feeding, toxicological and human studies.

# 9. Toxicological information

## 9.1. General considerations

Toxicological studies should be carried out with test material representative of the Novel Food as intended to be marketed, i.e. the test material should be manufactured according to the production process described in section 2, meet the compositional characteristics provided in section 3 and meet the specifications proposed in section 4. If this is not the case, a rationale should be provided to substantiate why the material used for the toxicological studies is representative of the novel food and appropriate for safety assessment.

Tests should be conducted in accordance with international guidelines (e.g. OECD) and according to the principles of Good Laboratory Practices (GLP).

The Panel notes that all relevant knowledge on the Novel Food should be considered in order to make decisions on whether and which toxicity studies are necessary. Important elements include:

- the identity, chemical structure, composition, and physico-chemical properties of the Novel Food (sections 1-4);
- available information on previous human consumption of the Novel Food and its source (section 5);
- anticipated use(s), maximum use levels and the resulting intakes (section 6);
- available toxicokinetic data (section 7);
- available toxicological data on the Novel Food or its constituents;
- available human studies

In case of insufficient data also

- (quantitative) structure activity relationship ((Q)SAR) data;
- toxicological data on structurally related substances ('read-across') should be considered.

The Panel considers that the tiered toxicity testing approach proposed for food additives should be considered as the default approach. It integrates the core areas of toxicokinetics, genotoxicity, repeated dose toxicity testing (subchronic, chronic toxicity and carcinogenicity) and reproductive and developmental toxicity (EFSA ANS Panel, 2012). Additional studies may be needed to examine specific biological processes which may not be fully considered in the core areas for evaluation. Other studies that may be relevant include immunotoxicity, hypersensitivity and food intolerance, studies on neurotoxicity, endocrine activity and mechanisms and modes of action.

Deviations from this approach and/or its non-applicability should be reasoned with sound scientific arguments based on the elements listed in the bullet points above.

The types and purposes of toxicity studies are outlined in sections 9.2 to 9.5 of the present Guidance for Novel Food applications. Particular cases are described in Section 9.6.

The Panel notes that the Threshold of Toxicological Concern (TTC) approach might be helpful when assessing the risk of low-exposure to substances such as impurities, metabolites and degradation products present in (or derived from) the Novel Food for which toxicity data may not be available. The applicant is advised to consult the EFSA Guidance on the concept of Threshold of Toxicological Concern (TTC) (EFSA SC, 2012b).

## 9.2. Genotoxicity

The assessment of genotoxic potential is a basic component of chemical risk assessment (EFSA SC, 2011b). Genotoxicity testing of Novel Foods should aim at identifying substances which could cause heritable damage in humans, and at predicting potential genotoxic carcinogens in cases where carcinogenicity data are not available.

The Scientific Committee recommended a step-wise (tiered) approach for the generation and evaluation of data on genotoxic potential (EFSA SC, 2011b). A basic battery of *in vitro* tests is recommended as a first step, and follow-up approaches in the event of positive results from the basic battery are provided. Recommendations on test types, results interpretations and other issues in testing the genotoxicity of substances present in food are described in detail in the Opinion of the Scientific Committee.

The Panel notes that the approach proposed by the Scientific Committee in principle applies to Novel Foods. For some complex mixtures and whole foods it may be necessary to focus on specific constituents of the Novel Food. Deviations can be argued on a case-by-case basis.

## 9.3. Subchronic toxicity

In line with the Guidance for food additives, a subchronic toxicity study should normally be submitted (EFSA ANS Panel, 2012). The major objective of such study is to identify any adverse effects following prolonged exposure via an appropriate oral route.

It should also allow determination of the relevant BMDL (EFSA, 2009) or the NOAEL. The subchronic toxicity study can provide indications for the need for additional studies on specific effects(section 9.4-5).

The study should normally be conducted for a period of at least 90 days (OECD TG 408), modified to include assessment of some additional parameters described in the more recent guideline on repeated-dose 28-day oral toxicity studies in rodents (OECD TG 407). The additional parameters place more emphasis on endocrine-related endpoints. The modified 90-day study should allow for the identification of substances with the potential to cause neurotoxic, immunological, reproductive organ effects or endocrine-mediated effects. When toxicokinetics testing indicates a lack of systemic availability, studies should at least investigate both pathological and physiological effects in the gastrointestinal tract. The effects of unabsorbed materials on gastrointestinal function and tolerance also need to be investigated. Specific to Novel Foods, the Panel notes that additional markers of potentially adverse nutritional and/or metabolic effects should be considered on a case-by-case basis, according to the available body of evidence and the nature of the Novel Food.

For 'whole foods', the testing requirements should be determined using a case-by-case approach as special considerations are required with regard to dose selection and the avoidance of possible nutritional imbalances. For further guidance on the conduction of subchronic oral toxicity studies with 'whole foods', the applicant is advised to consult the relevant Guidance from the Scientific Committee (EFSA SC, 2011c).

## 9.4. Chronic toxicity and carcinogenicity

Important considerations which can trigger the need for chronic toxicity or carcinogenicity studies include, among others, critical findings in the subchronic study as well as results of *in vitro* or *in vivo* toxicity tests, including genotoxicity tests. Further guidance on the triggers for these studies and their implementation are outlined in the Guidance on food additives (EFSA ANS Panel, 2012) and respective OECD Guidelines (OECD TG 451, 452 or 453).

## 9.5. Reproductive and developmental toxicity

Decisions on whether tests for reproductive and developmental toxicity are necessary need to be considered in the light of toxicokinetics and toxicity data, including read-across data.

Any indications of effects on reproductive organs or parameters, for example in the modified 90-day oral toxicity, will trigger testing for reproductive and developmental toxicity. Reproductive and developmental toxicity testing may not be required, if argued on a case-by-case basis.

## 9.6. Specific cases

### 9.6.1. Insects

The EFSA Scientific Committee has identified potential hazards related to the use of farmed insects as food (EFSA SC, 2015). These should be considered in applications for Novel Foods which consist of, are isolated from, or are produced from farmed insects, taking into account the species and substrate to be used, as well as methods for farming and processing. Insects collected from the wild may bear additional biological and chemical hazards which should be considered and addressed.

### 9.6.2. Microorganisms

A wide variety of bacterial and fungal species are used in food and feed production, either directly (e.g. to produce fermented foods) or as sources of additives, food enzymes or other components of foods. Many of them are present in high concentrations as viable bacteria in the final product. Some of these microorganisms have a history of safe use and have been assigned the qualified presumption of safety (QPS) status by EFSA which constitutes a preliminary safety assessment (EFSA BIOHAZ Panel, 2015). This QPS list includes taxonomic groups that have not raised safety concerns so far, and others for which some safety concerns exist but could be defined and addressed with "qualification" as expressed in the QPS list. Therefore, any strain of microorganism, the identity of which could be unambiguously established and assigned to a QPS group, would be freed from the need for an

exhaustive safety assessment other than satisfying the criteria and qualifications specified previously (EFSA, 2008) and assessing the risk of antimicrobial resistance (EFSA FEED 2012)

For those microorganisms for which safety properties are less well understood, a safety assessment should be provided. The safety assessment of microorganisms is primarily based on unambiguous taxonomic classification at species level and complete strain characterisation by fully assembled and validated whole-genome sequence analysis to enable the detection of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features (e.g. toxins, D-lactate, etc.). Phenotypic characterisation of the potential antimicrobial resistances (intrinsic or acquired) should also be carried out following EFSA recommendations applying to all microorganisms use in food or feed production (EFSA FEEDAP Panel, 2012). When appropriate depending on the taxonomic classification and genome information of the microorganism, other potentially adverse phenotypic features should be assessed (e.g. potential toxin production, haemolytic activity, infectivity, adverse immune effects, etc.). For safety assessment, information should be provided on the numbers of viable microorganisms in the final product and stability.

### 9.6.3. Engineered nanomaterials

Where the Novel Food containing or consisting of "engineered nanomaterials", the applicant should consider the Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain from EFSA's Scientific Committee (EFSA SC, 2011a).

## 9.7. Human data

Human studies, if available, should be provided if they contain information relevant for the safety assessment such as physical examination, blood chemistry, haematology, urine analysis, blood pressure and organ function tests and/or monitoring of adverse reactions. Relevant data may be derived from the use of the Novel Food for medical purposes or from epidemiological studies. Additional human studies may be needed to investigate further potentially adverse effects. In those cases where the Novel Food may exert pharmacodynamic effects, specific studies may be required to demonstrate that the proposed consumption and use of the Novel Food does not raise safety concerns.

The data from intervention studies and observational studies in humans should be organised according to a hierarchy of study designs and research question, reflecting the relative strength of evidence which may be obtained from different types of studies. Studies with the highest level of scientific evidence should be presented first.

# 10. Allergenicity

Food allergens are mostly (glyco)proteins, and thus the allergenic potential of a Novel Food containing no protein (or protein fractions) is very low. Methods of analysis for protein (including the limits of detection and quantification) and the results should be provided in section 2.

The default assumption for Novel Foods containing proteins is that such Novel Foods have allergenic potential. The allergenic potential of the Novel Food should be explored by considering its composition, particularly its protein(s), its source, the production process, and available experimental and human data. This comprises a comprehensive literature review in order to retrieve available information on sensitisation, and on case reports of allergic reactions and/or allergenicity studies (in vitro, in animals, in humans) of the Novel Food and/or its source(s).

Information on appropriate methods to further investigate the potential allergenicity of foods is provided by the NDA Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes (EFSA, 2014). Such methods include:

## 10.1. Protein analysis

- Protein content in the Novel Food
- Immunological tests (e.g. Western blotting)

- Molecular weight of the potentially allergenic protein, heat stability, sensitivity to pH, digestibility by gastrointestinal proteases,
- Degree of sequence homology with known allergens.

### 10.2. Human testing

- Detection of specific IgE antibodies
- Skin prick testing
- Double blind placebo controlled food challenge studies

If an applicant wishes to demonstrate that the Novel Food is unlikely to trigger adverse reactions in sensitive individuals under the proposed conditions of use, he should follow the approach outlined in the EFSA Guidance on the preparation and presentation of applications pursuant to Article 6 Paragraph 11 of Directive 2000/13/EC, as amended (EFSA, 2013).

Applicants for Novel Foods which potentially contain allergens listed in Annex II of Regulation (EU) No 1169/2011 and who seek exemption from mandatory labelling are advised to file an application pursuant to Article 21 paragraph 2 of Regulation 1169/2011 (previously Article 6 Paragraph 11 of Directive 2000/13/EC) by using the afore-mentioned guidance document (EFSA, 2013).

## Concluding remarks

The applicant should integrate the data presented in the previous sections to provide their overall considerations on how the information supports the safety of the Novel Food under the proposed conditions of use.

Where potential health hazards have been identified (e.g. on the basis of the composition of the Novel Food, its production process, its history of use, results from animal or human studies), they should be discussed in relation to the anticipated intakes of the Novel Food and proposed target populations.

In particular, the applicant should address:

- The relevance of toxicologically relevant components (e.g. impurities, by-products, residues, chemical or microbiological contaminants) in relation to their estimated intakes, possible background exposure and their health-based guidance values (e.g. tolerable daily intakes), when applicable.
- The results of toxicity studies.
- Any adverse effects identified through the human data.
- Sources of uncertainties.

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## Glossary and/or abbreviations

| | |
|---|---|
| ADI | Acceptable daily intake |
| NOAEL | No adverse effect level |
| OECD | Organisation for Economic Co-operation and Development |