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Guidelines of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the information required to perform the assessment of processing aids that are intended to be used in the preparation and production of food

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Abstract

The processing aids used in food preparation and production processes are regulated in Spain by Royal Decree 773/2023, which also defines them. There is also a specific regulation for the processing aids used in the production process of edible oils, which are regulated by Royal Decree 640/2015.

As established in said Royal Decrees, the processing aids that do not appear in Annex I, and that are not referred to in sections 2 and 3 of Article 3, of Royal Decree 773/2023, and the processing aids used in the production process of edible oils that do not appear in Annex I of Royal Decree 640/2015

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must be subject, for their approval and inclusion in said annexes, to a risk assessment by the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) that establishes the safety of the intended use.

In this regard, and in order to specify what information is necessary to evaluate the safety of the use of said processing aids and thus facilitate the submission of the assessment application dossiers, the AESAN Scientific Committee has developed these guidelines that are an amendment of those approved by the AESAN Scientific Committee in 2010, which they replace.

They establish a series of guidelines regarding the submission of processing aid assessment applications, in addition to the documentation that must accompany said applications, in the form of a dossier, which will include information regarding: administrative details and general presentation; detailed composition and specifications; stability and reactivity; authorised uses in human food; technological function; toxicological reference values; allergenicity; efficacy; residues and environmental impact.

Key words

Processing aids, assessment, guidelines, application, dossier.

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1. Introduction

Processing aids are necessary in many food production processes, facilitating them and being able to significantly influence the final quality or safety of food. These processing aids used in food preparation and production processes are regulated in Spain by Royal Decree 773/2023, which aims to establish the basic regulations in relation to the use of processing aids, the criteria of identity and purity that apply to said processing aids, their conditions of use and the mentions that must appear on their labelling (BOE, 2023a). Said Royal Decree defines processing aids as any substance that:

1. is not consumed as a food by itself,
2. is intentionally used in the processing of raw materials, foods or their ingredients to fulfil a certain technological purpose during treatment or processing, and
3. may result in the unintentional but technically unavoidable presence in the final product of residues of the substance or its derivatives provided they do not present any health risks and do not have any technological effect on the final product.

There is also a specific regulation for the processing aids used in the production process of edible oils, which are regulated by Royal Decree 640/2015 (BOE, 2015), which approves the list of processing aids authorised for the preparation of edible vegetable oils and their criteria of identity and purity, and which modifies Royal Decree 308/1983, which approves the Technical-Sanitary Regulations of Edible Vegetable Oils.

As established by Royal Decree 773/2023, processing aids that are not included in its Annex I, and that are not referred to in sections 2 and 3 of Article 3 of the aforementioned Royal Decree, must be subject, for approval and inclusion in said Annex I, to a risk assessment by the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) that establishes the safety of the intended use, following a favourable report from the General Directorate of the Food Industry of the Ministry of Agriculture, Fisheries and Food. Likewise, the processing aids used in the production process of edible oils, regulated by Royal Decree 640/2015, that do not appear in Annex I of this Royal Decree must also be subject, for their approval and inclusion in said Annex, to an assessment by the AESAN Scientific Committee, with a favourable prior report from the General Directorate of the Food Industry also being necessary.

In this regard, the AESAN Scientific Committee has developed these guidelines in order to specify what information is necessary to assess the safety of the use of the aforementioned processing aids and thus facilitate the submission of the assessment application dossiers.

It should be noted that those processing aids that are legally marketed in other Member States of the European Union, in accordance with the principle of mutual recognition, may be used in Spain for the same purpose, with the same restrictions and limitations that exist in other Member States. All of this without prejudice to the responsibility that food business operators have based on the provisions of Regulation (EC) No. 178/2002 (EU, 2002).

Likewise, and in accordance with the provisions of Royal Decree 773/2023, when a substance is authorised as a food additive, it may also be used as a processing aid, even if it does not appear in

the list of substances identified in Part B of Annex I of this Royal Decree, provided that compliance with the requirements contained in the definition of processing aids can be demonstrated.

These guidelines are an amendment of those approved by the ASEAN Scientific Committee in 2010 (AESAN, 2010), which they replace.

For the purposes of these guidelines, the term processing aid may correspond to either a single substance or a set of substances formulated in known proportions.

2. Submission of applications

In accordance with Royal Decree 697/2022, of 23 August, which approves the Statute of the Spanish Agency for Food Safety and Nutrition (BOE, 2022), requests for a report to the AESAN Scientific Committee must be submitted to it by the AESAN Governing Council.

Requests for a report on the safety of the use of a processing aid must be submitted to the Executive Directorate of AESAN so that, if appropriate, they are submitted to the Governing Council for valuation and, eventually, passed on to the Scientific Committee.

These applications must be accompanied by a dossier providing information on all the headings set out in section 3, the content of which is detailed in these guidelines. This information must be endorsed with experimental data obtained in accordance with current scientific and technological knowledge.

Likewise, the applications must contain a summary of the dossier, including a description of the studies submitted, as well as a general conclusion regarding the available data.

Before making the application, the applicant must check whether the product and the intended use actually correspond to a processing aid. Likewise, it must check if there are authorisations for the use of the same processing aid, under the same conditions and for the same purpose, in other countries of the European Union and if the substances present in the product are authorised for use in human food in any country.

It must also be checked if there are toxicological reference values established by national or international organisations, of all the components present in the processing aid, which allow estimating the risk of the consumer's exposure to its possible residues present in the destination food.

During the assessment of a particular dossier, the AESAN Scientific Committee may consider that, for the assessment of the processing aid, additional data or studies are necessary, not provided by these guidelines.

The assessments of the ASEAN Scientific Committee are public. For this purpose, only information relating to the production process of the processing aid may be considered confidential, upon request and, eventually, acceptance by the Committee.

3. Documentation required for the assessment of a processing aid

3.1 Administrative data and general presentation

- Name or business name and address of the applicant and the person responsible for the dossier.
- Name or business name and address of the manufacturer of the processing aid.
- Trade name of the processing aid.

- Chemical composition.
- Summary of the dossier and list of attached documents.

3.2 Detailed composition and specifications

3.2.1 Composition

- Complete composition of the processing aid, both as regards the active substances and their additives, stabilisers or any other co-formulation. This statement must include the names of the substances present in accordance with the IUPAC (International Union of Pure Applied Chemistry) nomenclature, common name, trade name, synonyms and CAS (Chemical Abstract Service) numbers (if available).
- Empirical and developed formula of each component that constitutes the processing aid.
- Physical state (liquid, powder…).
- Concentration in % of each component present in the processing aid.
- Production process of the processing aid.
- Solubility in the target food and/or, where appropriate, in the solvent of use.
- pH in solution for the concentration of use.
- Where appropriate, information on microbiological characteristics, in particular on the possible presence of pathogens, bacterial toxins or mycotoxins.
- Other data that the applicant considers useful for the characterisation of the product (for example, other physical or chemical properties).

3.2.2 Specifications

Specifications of the processing aid must be established, indicating the tolerance margins (±) or concentration ranges for each of its components. In addition, the most relevant impurities present or degradation products formed must be identified and their maximum limits established.

Once the specifications have been established, compliance must be demonstrated through the quantitative analysis of each component in at least three different batches of the processing aid, providing the certificates of the analysis results issued by the corresponding analysis laboratory.

The methods of analysis used must be standard methods (European Pharmacopoeia, United States Pharmacopoeia, the International Organization for Standardization (ISO) or the Association of Official Analytical Collaboration (AOAC) International) or other validated methods, and preferably accredited according to the UNE-EN ISO/IEC 17025 standard (UNE-EN, 2017). The dossier shall detail the operating parameters of the analytical methods, in particular the limit of detection and the quantification range. Chromatograms, spectrograms, etc., will also be included.

3.3 Stability and reactivity

3.3.1 Stability

Stability of the processing aid during its storage (specifying under what conditions its degradation occurs) and under the conditions (temperature, pH...) of food processing. This information must be accompanied by the relevant studies conducted with the processing aid object of the request.

3.3.2 Reactivity

Reactivity of the processing aid with respect to the contact environment, specifying the nature of the reactions and degradation products that may be formed in contact with the food or with other substances present during the food production process.

3.4 Authorised uses in human food

List of authorised uses in human food of the processing aid subject to application in other countries or, failing this, of each of its individual components. This information must be accompanied by the corresponding supporting documents.

3.5 Technological function

3.5.1 Alleged technological use

Description of the requested use for the processing aid, including the target food or foods.

3.5.2 Level of use

Description of the concentrations to be used of the processing aid for each use and target food. The concentrations of use of the processing aid will be established so that the amount used is limited to the minimum necessary to obtain the desired effect.

3.5.3 Description of the technological process

Detailed description of the process for which the use of the processing aid is envisaged, including aspects such as:

1. Forms of incorporation of the processing aid during the food production process:
- Phase of the process in which the processing aid is incorporated.
- Form in which the processing aid is incorporated and description of the dosing systems used.
- Methods of controlling the concentrations of the processing aid present in the process after dosing.
- Contact time of the processing aid with the food.
- Possibility of successive additions of the processing aid during the food production process.

2. Identification of the phases of elimination of the processing aid and its components during the food production process:
- Spontaneous elimination (e.g., by degradation, evaporation, etc.), or
- Intentional elimination by a process to be specified.

In the event that the use of the processing aid results in the presence of technically unavoidable residues in the food, the reasons (for example, technological) that prevent the elimination of these residues of the processing aid or its components during the food production process must be adequately justified.

3.6 Toxicological reference values

When assessing the risk to the consumer, the applicant must provide the available information on toxicological reference values established by a competent body (national or international) or, in its absence, values based on experimental or bibliographic toxicological data, in laboratory animals and/or humans. These values shall be provided for both the active substance(s) and their co-formulations, as well as for the products resulting from their degradation or their reaction with the matrices, when they are considered toxicologically relevant.

If no toxicological reference values are available for any of the components of the processing aid, the relevant toxicological studies must be conducted in order to generate this information (Table 1).

These toxicological studies must be designed on the basis of the guidelines of the Organisation for Economic Co-operation and Development (OECD) as well as the recommendations for the establishment of a dossier for the application of assessment of food additives issued by the European Food Safety Authority (EFSA) in 2012 and the Implementing Regulation (EU) 2020/1823 (EU, 2020). The approach proposed in the EFSA guidelines (EFSA, 2012) takes into account current animal welfare requirements by adopting an evidence-based strategy aimed at reducing the use of animals in experimental trials (3R: replacement, refinement, reduction). The reports and studies must be conducted under a quality assurance system and following Good Laboratory Practices (GLP).

To request the toxicological assessment, all known *in vitro* and *in vivo* studies with laboratory animals will be included, as well as data on humans, which provide knowledge on: 1) toxicokinetics, 2) genotoxicity, 3) subchronic and chronic toxicity, and carcinogenicity, 4) toxicity on reproduction and development, and additional studies of immunotoxicity, hypersensitivity, allergy, intolerance reactions, endocrine activity, and/or neurotoxicity may be required from time to time, allowing an adequate risk assessment. These four aspects will be assessed in accordance with the recommendations for the establishment of an EFSA food additive assessment application dossier (EFSA, 2012).

Table 1. Studies to be included in the toxicology dossier	
Toxicokinetics	The absorption, tissue distribution, metabolism and excretion of residues must be reported. Animal toxicokinetic and toxicity studies should be conducted using internationally agreed test guidelines, such as the OECD Test Guidelines (OECD TG) or the test methods of Regulation (EC) No. 440/2008 (EU, 2008). The most up-to-date edition of any test guide should be followed.
Toxicology	The studies must allow an assessment of the safety of the processing aid and its possible metabolites and degradation or reaction products with the matrices. **90-day subchronic oral toxicity study.** This study must be conducted on at least one animal species belonging to the order of rodents, according to OECD guideline TG 408 (OECD, 2018a). Or, a published study, conducted according to the most recent scientific requirements, may be provided to evaluate the safety of the processing aid (metabolites, degradation or reaction products with the matrices). **Reproductive toxicity study (including teratogenesis).** A one-generation reproductive toxicity study should be provided, according to OECD TG 415 (OECD, 1983) guidelines. However, if there are studies in the literature on each of the three segments (fertility and general reproductive capacity, embryofoetal toxicity and teratogenesis, peri- and postnatal toxicity), the applicant may submit them in his dossier replacing the one-generation reproduction study. The following supplementary studies shall be provided as relevant: **Carcinogenesis.** For any substance that has a similarity in its chemical structure with a known carcinogen or that has caused suspicious manifestations and/or lesions during the repeated administration toxicity study, according to the OECD guidelines TG 452 (OECD, 2018b). **Immunotoxicity.** The applicant shall consider the need for further studies concerning the effects of the substance on the immune system.
Genotoxicity	**Bacterial reverse mutation test** (OECD TG 471) (OECD, 2020). ***In vitro* mammalian cell micronucleus test** (OECD TG 487) (OECD, 2023). *In vitro* endpoints must be clearly negative to conclude with reasonable certainty that the substance does not present a genotoxic hazard. In the case of positive results of the basic test battery, it may be necessary to conduct further *in vitro* tests following EFSA's recommendations.

In the case of processing aids for which the usual toxicological studies cannot be conducted, either due to the instability of the chemical substances, or due to the very nature of the aid, information about their safety can be obtained from the final product, which has been prepared using this processing aid, under the intended conditions of use.

3.7 Allergenicity

The allergenic potential of the processing aid must be assessed taking into account its composition (particularly, in the event that its content includes proteins), the production process and the available data (experimental and human), including, in addition, information on cross-reactivity.

For this purpose, a complete literature review must be carried out in order to obtain the available information on the sensitisation, allergic reactions and/or allergenicity studies of the processing aid or its individual components.

If testing is necessary, the principles discussed in the EFSA Guidance on the allergenicity of GMO (Genetically Modified Organisms) should be followed when assessing allergenic components.

These principles for the determination of allergenicity include the investigation of structural aspects of the protein or peptide, *in silico* (or bioinformatic) approaches, IgE-binding and cell-based methods, analytical profiling techniques and animal models (EFSA, 2010).

3.8 Efficacy

3.8.1 Justification of use, interest and efficacy

It must be demonstrated that the product fulfils a certain technological purpose, and, therefore, conforms to the definition of processing aid. For this reason, it is necessary to explain the technological role of the processing aid, and to conduct efficacy studies through practical tests that demonstrate said efficacy.

3.8.2 Efficacy study

As a step prior to conducting the efficacy study, a protocol must be submitted detailing the proposed tests, including aspects such as the description of the conditions under which said tests will be conducted and the methodologies used.

A report will be prepared that includes the efficacy tests conducted, including in detail the protocols, methodologies, validations, results and associated conclusions.

The efficacy study will include representative tests of the real conditions, conducted under the same conditions without and with the proposed processing aid, in order to have reference samples for analysis. Thus, all tests must include a "control" test, which does not contain the processing aid under study.

The tests will be conducted with different concentrations of processing aid, in order to determine which is the minimum concentration that ensures its effectiveness. These tests at variable concentrations must also include sufficient sampling, in number and quantity, to allow the performance of a consistent treatment of the results. It is recommended to conduct out the tests with each of the different concentrations in at least three different batches of each target food.

The methods of analysis used must be standard methods (European Pharmacopoeia, United States Pharmacopoeia, the International Organization for Standardization (ISO) or the Association of Official Analytical Collaboration (AOAC) International) or other validated methods, and preferably accredited according to the UNE-EN ISO/IEC 17025 standard (UNE-EN, 2017). The report of the efficacy tests conducted will detail the operating parameters of the analytical methods.

Tests may be conducted in:

1. Laboratory conditions (on small quantities, in batch process) and/or under pilot conditions. Pilot conditions are understood as the simulation on a reduced scale of an industrial process, mimicking the technological conditions as closely as possible with respect to said process. If the industrial process for which the processing aid is intended is continuous, the tests under pilot conditions must be conducted continuously for a sufficiently long time to evaluate the impact of the use of the processing aid on the food and the process itself. They may be conducted discontinuously if the applicant can demonstrate that such a situation leads to a more unfavourable situation (less efficacy) than in the continuous case.

2. Industrial conditions, in the event that the processing aid is already used in another country, or in the event that the tests are conducted at the industrial level provided that the product resulting from said tests is not marketed.

The results from the efficacy tests of the processing aid may be compared with those obtained for other compounds or substances authorised for this use and in this food or in others. They may also be compared with the results of tests conducted with the processing aid itself within the framework of an application relating to other foods or processes.

The tests performed must allow determining:

- The efficacy of the processing aid for the proposed use.
- The concentration of processing aid, necessary and sufficient, to obtain the desired effect, and a proposed maximum concentration for use.

In the particular case of processing aids used for the bacterial disinfection of fruit and vegetable washing water, the quality requirements of the water used in the food company for the production of food, or that comes into contact with them or with materials and objects intended to come into contact with food, established in Royal Decree 3/2023 (BOE, 2023b), will be taken as a reference. According to this, the water must comply with the quality criteria established in Chapter II, Section 1st of the new Royal Decree and with the microbiological parameters and parametric values established in Annex I (*Escherichia coli*, intestinal enterococcus, *Clostridium perfringens*, *Legionella* spp.). The analysis methods used by the laboratories shall comply with the provisions of Annex III, Part C of said Royal Decree. The processing aids used for the bacterial disinfection of wash water in the food industry must, therefore, achieve the necessary efficacy to guarantee the water quality described in the Royal Decree. For the execution of the efficacy tests, the fruit or wash water shall be inoculated with the microorganisms specified in the Royal Decree in a concentration high enough to be considered representative of the most unfavourable scenario. Tests will be conducted with and without disinfectant, and samples will be taken under aseptic conditions of the washing water after inoculation and after washing the fruit. The process conditions must reproduce the real situation as much as possible. In particular, the dosage of processing aid, the contact time and the weight ratio of food/volume of washing solution will be reported and accurately reproduced.

3.9 Residues

As a step prior to carrying out the residue study, a protocol must be submitted detailing the proposed tests, including aspects such as the description of the conditions under which said tests will be conducted and the methodologies used.

A report will be prepared that includes the residue tests conducted, including in detail the protocols, methodologies, validations, results and associated conclusions.

As established in Royal Decree 773/2023, the use of processing aids may result in the involuntary, but technically unavoidable, presence in the final product of residues of the substance itself or its derivatives, provided that they do not present any health risk and do not have any technological

effect on the final product. As a general rule, therefore, it is necessary, whenever possible, to implement technological strategies to minimise the presence of the processing aid in the target food or foods.

3.9.1 Residue study

The dossier shall include residue tests on at least three different batches of the food or foods processed under conditions similar to those intended to be used before making such foods available to the consumer. The residues can be formed by the processing aid and, where appropriate, its degradation or reaction products with the matrix. The processing of the food may be reproduced on a laboratory or pilot scale, under conditions that reproduce as faithfully as possible the industrial conditions, or that lead to a more unfavourable situation of the presence of residues. In general, analyses of all the components of the processing aid will be conducted on the food at the time of addition (to corroborate the initial concentration), and on the food or foods produced, after processing (to corroborate their elimination or reduction).

The performance of residue tests on at least three batches of the food or processed foods will allow statistical analyses to be conducted that demonstrate the reduction of the concentration of the processing aid to technically unavoidable levels. In addition, these results will be the basis for the estimation of the corresponding exposure by the Scientific Committee.

The methods of analysis used must be standard methods (European Pharmacopoeia, United States Pharmacopoeia, the International Organization for Standardization (ISO) or the Association of Official Analytical Collaboration (AOAC) International) or other validated methods, and preferably accredited according to the UNE-EN ISO/IEC 17025 standard (UNE-EN, 2017). The report of the residue tests conducted shall detail the operating parameters of the analytical methods, in particular the limit of detection and the quantification range. Chromatograms, spectrograms, etc., will also be included.

In the particular case of tests on residues of processing aids used for the bacterial disinfection of fruit and vegetable washing water, the following must be taken into account:

- It must be justified that the concentration of residues of the processing aid in fruit and vegetables is technically unavoidable after having applied measures for its elimination. For example, performing a final rinse with drinking water.
- Likewise, the residue tests will use the contact time recommended by the manufacturer and will reproduce the recirculation of the wash water in the same terms as in the industrial process.
- Analysis of the residues of all components of the processing aid in wash water at the time of addition and after treatment, and in fruit or vegetables after removal of the processing aid, shall be presented.

3.10 Environmental impact

An assessment of the use of the processing aid in terms of environmental impact will be included, including aspects related to the possible residues of the processing aid in the environment.

3.11 Annexes and references

The complete studies and publications referred to in the application dossier will be provided.

4. Exposure estimation and risk characterisation

Based on the study of residues provided by the applicant, the Scientific Committee will make an estimate of the exposure of those residues through the consumption of the food or foods in which the processing aid has been used. For this purpose, food consumption data provided by validated national surveys, such as those included in the EFSA Comprehensive Food Consumption Database, will be taken into account.

The comparison of the estimated residue intakes against the toxicological reference values will allow the Scientific Committee to conclude on whether the use of the processing aid poses a concern for consumer health.

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