Guidance on the preparation and presentation of applications for exemption from mandatory labelling of food allergens and/or products thereof pursuant to Article 21 (2) of Regulation (EU) No 1169/2011

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SCIENTIFIC OPINION

Guidance on the preparation and presentation of applications for exemption from mandatory labelling of food allergens and/or products thereof pursuant to Article 21 (2) of Regulation (EU) No 1169/2011[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2]

European Food Safety Authority (EFSA), Parma, Italy

Endorsement date	**21 January 2021**
Implementation date	**27 March 2021**

ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on Scientific and technical guidance for the preparation and presentation of applications for exemption from mandatory labelling of food allergens and/or products thereof. This guidance applies to food ingredients or substances with known allergenic potential listed in Annex II of Regulation (EU) No 1169/2011 or products thereof, and aims to assist applicants in the preparation and presentation of well-structured applications for exemption from labelling. It presents a common format for the organisation of the information to be provided and outlines the information and scientific data which must be included in the application, the hierarchy of different types of data and study designs, reflecting the relative strength of evidence which may be obtained from different study types, and the key issues which must be addressed in the application in order to assess the likelihood of a food allergen-derived preparation/foodstuff(s) triggering adverse reactions in sensitive individuals under the proposed conditions of use. This guidance document was adopted by the NDA Panel in 2013 and updated in 2017 to reflect the application of Regulation (EU) No 1169/2011. Upon request from the European Commission in 2020, it has been revised to inform applicants of new provisions in the pre-submission phase and submission application procedure set out in Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain, that are applicable to all applications submitted as of 27 March 2021.

[1] The guidance was originally adopted on 10 October 2013 and updated on 14 March 2017 to reflect the application of Regulation (EU) No 1169/2011, which repeals Directive 2000/13/EC of the European Parliament and of the Council, and the publication of the scientific opinion of the NDA Panel on the evaluation of allergenic foods and food ingredients for labelling purposes in 2014. The present revision only aims to inform applicants of the new requirements set out in the General Food Law (Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain), and to guide to EFSA's practical arrangements implementing these new requirements. For this purpose, the revision concerns only the administrative part. The scientific content remains unchanged. The present guidance was endorsed on 21 January 2021 by the Panel on Nutrition, Novel Foods and Food Allergens (NDA): Dominique Turck, Jacqueline Castenmiller, Stefaan de Henauw, Karen-Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri and Marco Vinceti.

[2] As of 1 July 2018, it has been renamed Panel on Nutrition, Novel Foods and Food Allergens (NDA).

KEY WORDS

food allergens, allergenicity, foodstuff, exemption, labelling, application, guidance document

Panel members in 2013: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen.

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SUMMARY

Following a request from the European Commission (EC), EFSA was asked to deliver a scientific opinion on Scientific and technical guidance for the preparation and presentation of applications for exemption from mandatory labelling of food allergens and/or products thereof.

This guidance applies to food ingredients or substances with known allergenic potential listed in Annex II of Regulation (EU) No 1169/2011 or products thereof, hereafter referred to as food allergens. Food allergen-derived preparation refers to a product derived from a food allergen, and for which an exemption from labelling is requested. In this guidance, foods or beverages manufactured using (i.e. intentionally adding) food allergen-derived preparations, and for which an exemption from labelling is requested, are referred to as food allergen-derived foodstuffs**.**

The purpose of this guidance is to update the Commission guidelines in view of assisting applicants in the preparation and presentation of well-structured applications for exemption from labelling pursuant to Article 21(2) of Regulation (EU) No 1169/2011. It presents a common format for the organisation of the information to be provided and outlines the information and scientific data which must be included in the application, the hierarchy of different types of data and study designs, reflecting the relative strength of evidence which may be obtained from different study types, and the key issues which should be addressed in the application in order to assess the likelihood of a food allergen-derived preparation/foodstuff(s) triggering adverse reactions in sensitive individuals under the proposed conditions of use. This format will also help the EFSA NDA Panel to deliver its scientific advice in an effective and consistent way.

To allow a scientific evaluation by the EFSA NDA Panel of the likelihood that the food allergen-derived preparation/foodstuff(s) for which an exemption is requested triggers adverse reactions in sensitive individuals under the proposed conditions of use, the application must contain:

a) information on the characteristics of the food allergen-derived preparation for which the labelling exemption is requested. If the food allergen-derived preparation is intended for use in the manufacturing of foodstuff(s), information on the characteristics of the foodstuff(s) as consumed must be provided in the application. Where applicable, this information should contain aspects considered pertinent to the allergenic potential of the food allergen-derived preparation/foodstuff(s) for which an exemption is requested, such as the composition, physical and chemical characteristics, detailed description of the manufacturing process, stability, intended use, and an assessment of the residual allergenic proteins contained in the food allergen-derived preparation/foodstuff(s).

b) all pertinent scientific data which form the basis for the scientific evaluation of the allergenicity of the food allergen-derived preparation/foodstuff(s) for which an exemption from labelling is requested. Pertinent data means all human and non-human studies, published or unpublished, in favour and not in favour of the non-allergenicity of the food allergen-derived preparation/foodstuff(s) for the proposed use.

In cases where any of the required data are not relevant for a particular application, reasons/justification must be given for the absence of such data in the application.

Pertinent published human data should be identified through a comprehensive review which addresses the allergenicity of the food allergen-derived preparation/foodstuff(s) for the proposed conditions of use in a transparent manner. Data from food challenge studies in humans addressing the presence/absence of adverse reactions in susceptible (food allergic) individuals while consuming the food-allergen derived preparation/foodstuff(s) may provide important information regarding its allergenicity. Double-blind placebo controlled food challenges (DBPCFC) are less subject to bias than single-blind challenges or open challenges. Sufficient characterisation of the study population regarding the diagnosis of food allergy is important. The selected sample size should be adequately

justified within the context of each application. Because of the scientific uncertainties in extrapolating non-human data to humans, data from studies in animals or other model systems alone cannot substitute for human data as evidence of non-allergenicity, but may be included as supporting evidence.

Upon request from the European Commission in 2020, the guidance has been revised to inform applicants of new provisions set out in Regulation (EC) No 178/2002[3] (i.e. the General Food Law, hereafter GFL Regulation), as amended by Regulation (EU) 2019/1381[4], hereafter Transparency Regulation. They concern requirements in the pre-submission phase and submission application procedure that are applicable to all applications submitted on or after 27 March 2021:

- possibility to request general pre-submission advice (Article 32a(1) of GFL Regulation);
- mandatory notification of information related to studies commissioned/carried out on or after 27 March 2021 (Article 32b of GFL Regulation);
- publication of non-confidential version of all information submitted in support of the application and related confidentiality decision-making process (Articles 38 and 39-39e of the GFL Regulation);
- public consultation on submitted applications (Article 32c(2) of GFL Regulation).

For detailed information, please refer to EFSA's Practical Arrangements on pre-submission phase and public consultations[5] and EFSA's Practical Arrangements concerning transparency and confidentiality[6].

Applicants should also note that as of 27 March 2021, applications must be submitted using the e-submission system accessible through the European Commission website or the EFSA's website.[7]

Before submitting an application, applicants are also recommended to consult the EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021a).

Before submitting an application, applicants are also recommended to consult the EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021a) and the EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA 2021d).

This revised guidance applies to all applications submitted as of 27 March 2021 and should be consulted for the preparation of applications intended to be submitted from that date onwards.

[3] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[4] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[5] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[6] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

[7] https://www.efsa.europa.eu/en/applications/toolkit

It is intended that the guidance will be further updated as appropriate in the light of experience gained from the evaluation of applications for exemption from labelling.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION IN 2013

Article 6 Paragraph 11 of Directive 2000/13/EC, as amended by Directive 2003/89/EC, establishes the cases and conditions for amending Annex IIIa to that Directive, which includes a list of food ingredients or substances known as likely to trigger adverse reactions in sensitive individuals. These products must always appear in the list of ingredients on food labels.

The same Directive also sets up a procedure for exempting from labelling, under certain conditions, derivatives of these ingredients or substances. Applicants who are seeking the exclusion of a given product from Annex IIIa (i.e. exemption from labelling) have to submit a request supported by the results of relevant scientific studies.

The legislation, however, does not specify the content of such requests. Therefore, the Commission services established in 2005, in close cooperation with EFSA, an administrative guidance document specifying in a very succinct way what type of information the application should contain.

In the light of the experience gained with the evaluation of applications for exemption from labelling, and to further assist applicants in preparing and submitting their applications, the Commission deems it important to update the above-mentioned guidance document. In particular, in relation to the technical dossiers to be submitted, it appears useful to provide guidance as to which type of scientific data and information could be expected to substantiate the unlikelihood of adverse reactions triggered in susceptible individuals by the consumption of food ingredients or substances with known allergenic potential under the conditions of use specified by the applicants.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION IN 2013

On the basis of Article 29 of Regulation (EC) No 178/2002, EFSA is requested to advise on the scientific data and information expected to be provided by the applicants, in view of improving and updating by the Commission the guidelines for the submission and preparation of applications pursuant to Article 6 Paragraph 11 of Directive 2000/13/EC.

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION IN 2020

The European Commission (EC) requested EFSA to update the Guidance on the preparation and presentation of applications pursuant to Article 21(2) of Regulation (EU) No 1169/2011[8] in order to align it to Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain[9], which applies as from 27 March 2021.

The guidance document has been identified to require updating as regards its administrative part. This request does not cover the scientific part of the document that has been left unchanged.

[8] https://www.efsa.europa.eu/en/efsajournal/pub/3417

[9] Regulation EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC (OJ L 231, 6.9.2019, p. 1)

OBJECTIVES

The guidance presented in this document is for updating the Commission guidelines in view of assisting applicants in the preparation and presentation of well-structured applications for exemption from labelling pursuant to Article 21(2) of Regulation (EU) No 1169/2011.[10]

It presents a common format for the organisation of the information to be provided and outlines:

- the information and scientific data which must be included in the application,
- the hierarchy of different types of data and study designs, reflecting the relative strength of evidence which may be obtained from different study types,
- the key issues which should be addressed in the application in order to assess the likelihood of a food ingredient or substance triggering adverse reactions in sensitive individuals under the proposed conditions of use.

It is intended that the guidance will be further updated as appropriate in the light of experience gained from the evaluation of applications for exemption from labelling.

SCOPE

The guidance presented in this document is to assist applicants in preparing and presenting applications for exemption from labelling pursuant to Article 21(2) of Regulation (EU) No 1169/2011, which prescribes that the list of ingredients in Annex II shall be systematically re-examined and, where necessary, updated on the basis of the most recent scientific knowledge. This guidance is not intended for requesting other type of updates of Annex IIIa (e.g. addition of new ingredients).

GENERAL PRINCIPLES

1. This guidance is to be read in conjunction with the above-mentioned Regulation, as well as with Regulation (EU) 2019/1381[11] (hereinafter 'Transparency Regulation') amending *inter alia* Regulation (EC) No 178/2002[12] (i.e. the General Food Law, hereinafter 'GFL Regulation'), and with EFSA's Practical Arrangements[13] implementing the Transparency Regulation. In case of discrepancy between the content of this document and applicable legal acts, or EFSA's Practical Arrangements, the legal acts and the latter prevail. Before submitting an application, applicants are recommended to consult the EFSA Administrative

[10] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304. 22.11.2011, p.18.

[11] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[12] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[13] See EFSA's Practical Arrangements are available online at: https://www.efsa.europa.eu/en/corporate/pub/tr-practical-arrangements

guidance for the processing of applications for regulated products (EFSA 2021a) and the scientific opinion of the NDA Panel on the evaluation of allergenic foods and food ingredients for labelling purposes[14]. This guidance applies to food ingredients or substances with known allergenic potential listed in Annex II of Regulation (EU) No 1169/2011 or products thereof. The term **food allergen** will be used for all substances listed under Annex IIIa, being aware that lactose and sulphites are not food allergens, and that gluten may induce both food allergy and coeliac disease.

Food allergen-derived preparation (e.g. potassium caseinate), for which an exemption from labelling is requested, means a product derived from a **food allergen** (e.g. milk).

Foods or beverages (e.g. white wine) for which an exemption from labelling is requested that are manufactured using (i.e. intentionally adding) the **food allergen-derived preparation** (e.g. potassium caseinate) are referred to as **food allergen-derived foodstuffs** in this guidance**.**

Allergenicity refers to the capacity of the **food allergen-derived preparation/foodstuff(s)** to trigger adverse reactions in susceptible (food allergic) individuals when consumed orally under the specified conditions of use.

Allergenic protein refers to proteins or peptides (e.g. ovalbumin and lysozyme) responsible for the allergenicity of **food allergens** (e.g. egg).

2. The term **application** hereafter means a stand-alone dossier containing the information and the scientific data submitted for exemption from labelling of a food allergen-derived preparation/foodstuff(s) under the proposed conditions of use.

3. This guidance presents a common format for the organisation of the information in order to assist applicants in the preparation of a well-structured application. Adherence to this format will also facilitate access to the information by the EFSA NDA Panel in order to conduct the evaluation and deliver scientific advice in an effective and consistent way.

4. The EFSA NDA Panel evaluates the likelihood of adverse reactions in sensitive individuals after oral consumption of the food allergen-derived preparation/foodstuff(s) for which the labelling exemption is requested according to the nature and quality of the totality of the evidence provided. This includes information about the characteristics of the food allergen-derived preparation/foodstuff(s), its intended use, and the residual allergenic proteins it contains, as well as information on its residual allergenicity. There is no pre-established formula as to how much or what type of information is required to conclude on the non-allergenicity of the food allergen-derived preparation/foodstuff(s) for which the labelling exemption is requested. Scientific requirements are considered by the EFSA NDA Panel on a case-by-case basis and are to be found in published opinions relative to previous applications for exemption.

5. It is the duty of the applicant to provide all pertinent scientific data in the application (published and unpublished data, data in favour and not in favour) relative to the assessment of the likelihood of adverse reactions being triggered in sensitive individuals by the oral consumption of the food allergen-derived preparation/foodstuff(s) under the proposed conditions of use.

[14] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. EFSA Journal 2014;12(11):3894, 286 pp. doi:10.2903/j.efsa.2014.3894

6. Where some of the information and data required by this guidance are not included in a particular application, reasons/justifications must be provided.

7. The application must contain information on the characteristics of the food allergen-derived preparation for which an exemption from labelling is requested. If the food allergen-derived preparation is intended for use in the manufacturing of a foodstuff(s), information on the characteristics of the food allergen-derived foodstuff(s) must be provided. Where applicable, this information should contain aspects such as the composition, physical and chemical characteristics, manufacturing process, and stability.

   Measurements should be performed in a competent laboratory. Whenever a quality system is in place for performance/control/documentation (e.g. good manufacturing practice (GMP), good laboratory practice (GLP), applicable ISO standard), the particular system should be indicated.

8. The application must contain a detailed description of the conditions under which the food allergen-derived preparation/foodstuff(s) is intended to be used, including the corresponding use levels and exposure data (amount consumed on a single occasion).

9. The application must contain a detailed description of the manufacturing process of the food allergen-derived preparation and, if appropriate, of the food allergen-derived foodstuff(s) which has been manufactured from it, as consumed, including any steps introduced in the process to reduce the quantity of allergenic proteins in the food allergen preparation/foodstuff(s), or their allergenicity.

10. The application should contain an analysis of all residual major[15] allergenic proteins contained in the food allergen-derived preparation and, if appropriate, of all residual major allergenic proteins in the food allergen-derived foodstuff(s) which has been manufactured from it, as consumed. The protocol used to obtain the samples for analysis and the analytical methods used for the detection of allergenic proteins should be adequately described. Analytical methods need to be standardised and validated to ensure quality and consistency of the data. If no allergenic proteins are detected, this information on its own does not necessarily imply the non-allergenicity of the food allergen-derived preparation/foodstuff(s).

11. Data from food challenge studies in humans addressing the presence/absence of adverse reactions in susceptible (food allergic) individuals while ingesting the food allergen-derived preparation or foodstuff(s), whichever is intended for human consumption, may provide important information regarding its allergenicity. Double-blind placebo controlled food challenges (DBPCFC) are less subject to bias than single-blind challenges or open challenges. Sufficient characterisation of the study population regarding the diagnosis of food allergy/intolerance is important. The reasons for selecting a particular sample size in the context of each application should be indicated. Other human studies which do not entail oral consumption of the food allergen-derived preparation/foodstuff(s) (e.g. skin-prick testing studies) can be used as supportive evidence of non-allergenicity. Observational studies (e.g. case-reports) in humans consuming the food allergen-derived preparation/foodstuff(s), if available, should also be provided.

    It is not within the scope of this guidance to provide details on how food challenges should be performed, or on which clinical outcomes should be considered. For this, the NDA Panel considers what is generally accepted in the research field and consults experts in the discipline, as appropriate.

[15] For example, for the food allergen-derived preparation egg white, the major allergenic proteins ovomucoid, ovalbumin, conalbumin and lysozyme should be measured.

Because of the scientific uncertainties in extrapolating non-human data to humans, data from studies in animals or other model systems alone cannot substitute for human data as evidence of non-allergenicity, but may be included as supporting evidence.

Whenever a quality system has been used in the conduct of the studies (e.g. good clinical practice (GCP), good laboratory practice (GLP), applicable ISO standard), the particular system used should be indicated.

12. A comprehensive review of published human studies reporting on adverse reactions to the food allergen under the proposed use is required. The review should be performed in a transparent manner in order to demonstrate that the application adequately reflects all the evidence available.

    Data from studies in humans should be organised according to a hierarchy of study designs, and should reflect the relative strength of evidence which may be obtained from different types of studies.

13. One application should be prepared for each individual food allergen-derived preparation. In this context, if several preparations of the food allergen exist, only one can be the subject of each application. However, multiple foodstuffs manufactured using the same food allergen-derived preparation can be proposed by the applicant in the same application as candidates for labelling exemption, provided that the scientific evidence is valid for all proposed food allergen-derived foodstuffs[16].

14. Transparency and confidentiality (Articles 38 and 39-39e of the GFL Regulation). This is to be read in conjunction with Union law and case law, as well as with EFSA's Practical Arrangements concerning transparency and confidentiality (EFSA 2021c), available on the EFSA's website, which provide a comprehensive description of applicable procedures and provision.

    The Transparency Regulation introduced a general principle of proactive disclosure and transparency of information and data submitted to EFSA for scientific evaluation. In the light of this principle, and of the related provisions, EFSA must proactively disseminate all information shared by applicants for the purposes of EFSA's scientific assessment of regulated products, including that submitted during the assessment process. Specifically, EFSA is to make publicly available[17] *inter alia* the following information[18]:

    - all its scientific outputs;
    - scientific data, studies and other information supporting applications, including supplementary information, as well as other scientific data and information supporting requests from the Commission and the Member States for a scientific output;

[16] For example, if multiple milk-derived preparations exist (e.g. potassium caseinate, skimmed milk) for the same use (e.g. manufacture of wine), only one (e.g. either potassium caseinate or skimmed milk) can be the subject of an application. However, different types of wine (e.g. white and red) manufactured using the same preparation (e.g. same potassium caseinate preparation) under the proposed conditions of use can be proposed in the same application for labelling exemption.

[17] The proactive disclosure of the above information does not imply permission or licence for their re-use, reproduction, or exploitation in breach of the relevant existing rules concerning intellectual property rights or data exclusivity. EFSA cannot be held liable or responsible for any use of the disclosed data by third parties in breach of any existing intellectual property rights.

[18] For an exhaustive list of the types of information, documents or data which is made proactively available, please refer to Articles 5 and 6 of the Decision of the Executive Director of the European Food Safety Authority Laying down practical arrangements concerning transparency and confidentiality (EFSA 2021c).

- the information on which its scientific outputs are based;
- a summary of the advice provided to potential applicants at pre-submission phase, if applicable.

By derogation from the general principle of proactive disclosure and transparency, EFSA may grant confidential status to certain elements of applications dossiers, provided applicants submit a verifiable justification, and EFSA accepts the confidentiality request.

For this purpose, and for each document for which confidentiality is requested, the applicants are required to upload in the e-submission system:

- **a request to treat certain item(s) as confidential**, specifying: the confidentiality ground(s) and conditions, justification, excerpt of the text, location in the file.
- **a version of the concerned document with all information visible and no blackening applied**. In this version, all information claimed to be confidential by the applicant should be boxed or earmarked (confidential version, not for public disclosure);
- **a non-confidential version with all elements claimed to be confidential blackened** (public version).

The non-confidential (public) version of the dossier will be made publicly available in the OpenEFSA portal[19] as soon as the application is declared valid. The items on which confidentiality requests may be made are set out in Article 39(2) of the GFL Regulation. The decision on confidential treatment of information follows the procedure set out in Articles 39-39e of the GFL Regulation.

STRUCTURE OF THE DOSSIER

The following information should be provided in the application, and the structure should follow the pre-filled table of content required by the e-submission system available through the EFSA's[20] and European Commission's websites, to be used for submitting the application. Data provided in the application should be organised as follows:

ADMINISTRATIVE DATA

The following information should be provided in the application:

- Applicant's contact details (name of entity, email, address, post-code, phone, country, website)[21];
- Person responsible for the dossier contact details (name of person responsible/representative, name of entity, email, address, post-code, phone, country, website)[22];
- Manufacturer's contact details (name of entity, email, address, post-code, phone, country, website);
- Subject of the request (for which an exemption from labelling is requested);
- Existing authorisations at Member States level (country, status, reference of the authorisation);
- Existing authorisations in non-EU countries (country, status, reference of the authorisation);

[19] https://open.efsa.europa.eu
[20] https://www.efsa.europa.eu/en/applications/toolkit
[21] In case more than one company or organisation submits an application, provide their names and addresses. EFSA requires that only one contact person be authorised to communicate with EFSA.
[22] To facilitate communication, EFSA requires that there be only one contact person per application.

- Information on data sharing agreement in place, if any;
- Cover Letter, specifying the content of the submission.

PUBLIC SUMMARY

A short summary of the dossier should be provided. This document will be made available to the public and should not contain any confidential information. The public summary will be published together with the non-confidential version of the dossier on the OpenEFSA portal.

TECHNICAL DOSSIER[23]

It should include:

Pre-application information
All relevant pre-application identification(s) received by EFSA in the pre-submission phase for the regulated product which is the subject matter of the application and information required with regard to notification of studies obligation should be provided.

General/Scientific Information

- Specifications, including conditions of use and exposure data.
- Information specific to the food allergen-derived preparation, and to the food allergen-derived foodstuff(s) if applicable, for which an exemption is requested regarding the characteristics (such as the composition, physical and chemical characteristics, manufacturing process, and stability) and allergenic protein content.
- All scientific data (published and unpublished, in favour and not in favour) relative to the residual allergenicity of the food allergen-derived preparation, and of the food allergen-derived foodstuff(s) if applicable, under the proposed conditions of use.
- The glossary or abbreviation of terms quoted throughout the technical dossier, copies of publications, and full study reports of unpublished data.

Where some of the information/data required by this guidance are not included in a particular dossier, reasons/justification must be given for the absence of such data in the dossier.

List of annexes and references
A list of all the published studies and annexes submitted in support of the application should be provided, and uploaded in the e-submission system. Applicants are advised to list the references by section. For more details, see also section 4 of this guidance.

[23] Please see General principle 14.

GENERAL/SCIENTIFIC INFORMATION[24]

1. SPECIFICATIONS

1.1. Food allergen-derived preparation

Specify the food allergen-derived preparation for which an exemption from labelling is requested. If the name of the food allergen-derived preparation differs from those listed in Annex IIIa as amended, the food allergen as listed in Annex IIIa should also be specified[25].

1.2. Conditions of use

Specify whether the food allergen-derived preparation will be consumed as such and/or will be used in the manufacturing of foodstuff(s). In the latter case, specify the foodstuff(s) that will be manufactured using the food allergen-derived preparation.

1.3. Anticipated intake/exposure

Specify the expected quantity and pattern of consumption of the food allergen-derived preparation. If applicable, specify the expected quantity and pattern of consumption of the food allergen-derived foodstuff(s) for which an exemption from labelling is requested.

Information on the expected quantity of consumption per single occasion, on the pattern of consumption (e.g. times per day, time span in which a certain amount is consumed), and on particular conditions in which the food allergen-derived preparation/foodstuff(s) is meant to be consumed (e.g. before/during/after intense physical exercise) should be specified on an individual basis in different age groups.

2. CHARACTERISTICS OF THE FOOD ALLERGEN-DERIVED PREPARATION/ FOODSTUFF(S)

2.1. Food allergen-derived preparation

The food allergen-derived preparation for which an exemption is requested should be characterised. If several preparations derived from the food allergen exist, please clarify the specific preparation of the food allergen that is the subject of this application.

Please note that one application should be prepared for each individual food allergen-derived preparation[26].

2.1.1. General specifications

The source and specifications (e.g. physical and chemical properties, composition, and where applicable, microbiological constituents) of the food allergen-derived preparation for which an exemption is requested should be provided.

Analytical methods applied should be scientifically sound, standardised and validated to ensure quality and consistency of the data.

[24] Please see also General principle 14.

[25] For example, if exemption from labelling is requested for potassium caseinate, milk should be specified as the food allergen listed in Annex IIIa.

[26] For example, if multiple milk-derived preparations exist (e.g. potassium caseinate, skim milk) for the same use (e.g. manufacture of wine), only one (e.g. either potassium caseinate or skim milk) can be the subject of an application.

Measurements should be performed in a competent laboratory. Whenever a quality system is in place for control/documentation (e.g. GLP and ISO17025) the particular system should be indicated.

2.1.2. Manufacturing process

Where applicable, a detailed description of the manufacturing process should be provided. If the production follows a quality process (e.g. GMP) the particular system should be indicated. Please specify whether the manufacturing process is mandatory or refers to a voluntary code.

Any steps introduced in the process which could reduce the quantity of allergenic proteins or their allergenicity in the food allergen-derived preparation should be described in detail.

2.1.3. Allergen specifications

An assessment of all major residual allergenic proteins contained in the food allergen-derived preparation should be provided. Data/a rationale for the selection of the allergenic proteins to be measured should be provided.

Analytical methods applied should be scientifically sound, standardised and validated to ensure quality and consistency of the data for detection of residual allergenic proteins.

Details on the protein extraction method used and the conditions applied should be described. Attention should be paid to whether the extraction methods used are appropriate for the matrix of interest.

Details on the performance of the method used for detecting allergenic proteins should be provided in terms of accuracy, precision, limit of detection (LOD), recovery, and limit of quantification (LOQ) whenever possible (e.g. whenever certified reference materials are available). Cross-reactivity should be considered.

2.1.4. Stability

Where applicable, a brief summary of the studies undertaken to assess the stability of the food allergen-derived preparation (e.g. conditions, batches and analytical procedures) should be provided. Conclusions with respect to storage conditions and shelf-life should be given. Batch-to-batch variability should be addressed.

2.2. Food allergen-derived foodstuff(s)

If the food allergen-derived preparation for which an exemption is requested is intended for use in the manufacturing of a foodstuff(s), information on the characteristics of the food allergen-derived foodstuff(s) as consumed should be provided in the application.

If multiple foodstuffs manufactured using the same food allergen-derived preparation are proposed as candidates for labelling exemption, please provide the information below for each of the proposed food allergen-derived foodstuffs.

2.2.1. General specifications

The source and specifications (e.g. physical and chemical properties, composition, and where applicable microbiological constituents) of the food allergen-derived foodstuff(s) for which an exemption is requested should be provided.

Analytical methods applied should be scientifically sound, standardised and validated to ensure quality and consistency of the data.

Measurements should be performed in a competent laboratory. Whenever a quality system is in place for control/documentation (e.g. GLP and ISO17025) the particular system should be indicated.

2.2.2. Manufacturing process

Where applicable, a detailed description of the manufacturing process should be provided. If the production follows a quality process (e.g. GMP), the particular system should be indicated. Please specify whether the manufacturing process is mandatory or refers to a voluntary code.

Any steps introduced in the process (e.g. heating, high pressure, ultrasound, fermentation, digestion, and filtration) which could affect the quantity of allergenic proteins or their allergenicity in the food allergen-derived foodstuff(s) should be described in detail.

2.2.3. Allergen specifications

An assessment of all major residual allergenic proteins contained in the food allergen-derived foodstuff(s) should be provided by using direct methods for allergen detection whenever possible (e.g. ELISA, and mass spectrometry). Data/a rationale for the selection of the allergenic proteins to be detected should also be provided. Indirect methods for allergen detection (i.e. for DNA analysis, e.g. PCR) may be used in addition, or whenever direct methods are not available (e.g. celery) or not suitable (e.g. extensive heat treatments) for allergen detection.

Analytical methods applied should be scientifically sound, standardised and validated to ensure quality and consistency of the data for detection of residual allergens. A rationale for the selection of the methods of detection used in the context of a particular application should be provided.

Details on the protein/DNA extraction method used and the conditions applied should be described. Attention should be paid to whether the extraction methods used are appropriate for the matrix of interest.

Details on the performance of the detection method(s) should be provided in terms of accuracy, precision, limit of detection (LOD), recovery, and limit of quantification (LOQ) whenever possible (e.g. whenever certified reference materials are available). Cross-reactivity should be considered.

2.2.4. Stability

Where applicable, a brief summary of the studies undertaken to assess the stability of allergenic proteins in the food allergen-derived foodstuff(s) (e.g. conditions, batches and analytical procedures) should be provided. Conclusions with respect to storage conditions and shelf-life should be given. Batch-to-batch variability should be addressed.

3. SCIENTIFIC DATA ON ALLERGENICITY

All pertinent scientific data relative to the allergenicity of the food allergen-derived preparation/foodstuff(s) for which an exemption is requested should be provided. Pertinent data means all human and non-human studies, published or unpublished, in favour and not in favour of the non-allergenicity of the food allergen-derived preparation/foodstuff(s) for the proposed use.

Reporting of primary data should be transparent, complete, and unambiguous, in order to allow for a full scientific evaluation. In this context, journal abstracts and articles published in newspapers, magazines, newsletters or handouts that have not been peer-reviewed, books or chapters of books for

consumers or the general public, and posters or abstracts of conference proceedings **do not generally meet** the reporting standards required for a scientific evaluation and should not be quoted.

3.1. Identification of pertinent data

3.1.1. Identification of published human data

Published human data should be identified through a comprehensive review which addresses the allergenicity of the food allergen-derived preparation/foodstuff(s) for the proposed use in a transparent manner.

The following information on the comprehensive review should be provided, as appropriate:

3.1.1.1. Authorship

The name, affiliation, declaration of interests in relation to the subject covered by the review, and signature of the reviewer(s) responsible for the comprehensive review should be indicated.

3.1.1.2. Background

The suitability (strengths and limitations) of the proposed search strategy to retrieve all available information on the allergenicity of the food allergen-derived preparation/foodstuff(s) for the proposed use should be discussed here.

3.1.1.3. Exclusion and inclusion criteria

Exclusion and inclusion criteria that have been applied by the applicant in order to select the pertinent publications.

3.1.1.4. Literature search

The databases that have been searched should be listed, and details about the search strategy (including the terms used, limits used such as dates of publication, publication types, languages, population subgroups or default tags) should be provided. Other sources of data should be acknowledged (web sites, hand searching, etc.).

A list of references (but not copies/reprints) of the publications considered as NOT PERTINENT to the application and therefore **excluded** should be provided (alphabetical order of first authors).

For pertinent published human data identified, please go to Section 3.2.

3.1.2. Identification of unpublished human data

The strategy followed to identify unpublished human studies that are considered as pertinent to the application should be depicted.

For pertinent unpublished human data identified, please go to Section 3.2.

3.1.3. Identification of published and unpublished non-human data

The strategy followed to identify published and unpublished non-human studies that are considered as pertinent to the application should be depicted, and the reasons for selecting them as supporting evidence should be stated.

For pertinent published and unpublished non-human data identified, please go to Section 3.2.

3.2. Pertinent scientific data identified

A list of references of the pertinent published and unpublished studies (by alphabetical order of first authors, clearly indicating the publication status) should be provided in the sections below in accordance with the hierarchy of study design and publication type.

Evidence required by the applicable legal act and full study reports of unpublished studies should be provided as indicated in Section 4.

3.2.1. Human intervention studies

3.2.1.1. Food challenge studies

- Double-blind placebo controlled food challenges
- Single-blind placebo controlled food challenges
- Open label food challenges

3.2.1.2. Skin prick testing studies

3.2.1.3. Other

3.2.2. Human observational studies

3.2.2.1. Case reports

3.2.2.2. Retrospective or recall studies

3.2.3. Animal studies

3.2.4. In vitro studies

3.2.4.1. IgE-binding capacity analysed by inhibition studies

3.2.4.2. Other

4. REFERENCES AND ANNEXES TO THE DOSSIER

Electronic copies of all pertinent studies (published and unpublished, proprietary and not proprietary) submitted in support of the dossier, including electronic copies of protocols and full study reports of

clinical studies unpublished and/or proprietary to applicant should be uploaded in the e-submission system as part of the technical dossier.

EFSA strongly recommends that each document, including annexes (i.e. study reports, raw data, published studies and any other document in the technical dossier) be electronically searchable and accessible to allow downloading and printing of the file. This applies to all documents or information uploaded as part of the initial submission, or later during the risk assessment process.

The applicant must ensure that terms and conditions asserted by any rightsholder of studies, information or data submitted to EFSA are fully satisfied. The applicant may consult with copyright licensing authorities (i.e. at national level) for guidance on purchasing the appropriate licenses to provide studies, information or data to EFSA, taking into account the proactive disclosure requirements as detailed above. For publications already available to the public upon payment of fees (e.g. studies published in scientific journals) for which the applicant does not have or cannot obtain intellectual property rights for the purposes of the proactive public disclosure requirements, the applicant must provide (a) a copy of the relevant publications along with the relevant bibliographic references/citations for scientific assessment purposes only, in the confidential version of its application and (b) these relevant bibliographic references/citations where these publications are available to the public in the non-confidential version of its application for public dissemination on the OpenEFSA portal[27].

4.1. Information on study notifications in accordance to Article 32b of GFL Regulation

Applicants should provide via the e-submission system information related to all studies, commissioned/carried out as of 27 March 2021 to support an application, and notified via the database available on the EFSA's website.[28]

The practical arrangements on pre-submission phase and public consultations provide full overview of the requirements for notification of studies (EFSA 2021b).

[27] https://open.efsa.europa.eu
[28] https://www.efsa.europa.eu/en/applications/toolkit

GLOSSARY AND ABBREVIATIONS

Note: The definitions given in this glossary are valid only for the purpose of this guidance document.

Allergenicity	The capacity of a food allergen to trigger adverse reactions in susceptible (food allergic) individuals when consumed orally under the specified conditions of use.
Allergenic protein	Proteins or peptides responsible for the allergenicity of food ingredients or substances listed in Annex II of Regulation (EU) No 1169/2011.
Applicant	Refers to the natural or legal person responsible for the submission and content of the application, and for the interaction with regulatory authorities in the course of the evaluation.
Application	Stand-alone dossier containing the information and scientific data submitted for exemption from labelling pursuant to Article 21(2) of Regulation (EU) No 1169/2011, of a food allergen-derived preparation/ foodstuff(s) under the proposed conditions of use.
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
Food allergens	Food ingredients or substances with known allergenic potential listed in Annex II of Regulation (EU) No 1169/2011 or products thereof.
Food allergen-derived foodstuffs	Foods or beverages that are manufactured using (intentionally adding) food allergen-derived preparations, and for which an exemption from labelling is requested.
Food allergen-derived preparation	Product derived from a food allergen, and for which an exemption from labelling is requested
GCP	Good clinical practice
GFL	General Food Law
GLP	Good laboratory practice
GMP	Good manufacturing practice
LOD	Limit of detection
LOQ	Limit of quantification
PCR	Polymerase chain reaction
TR	Transparency Regulation

REFERENCES

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EFSA (European Food Safety Authority), 2021c. Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality. Available online: https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-transparency-and-confidentiality.pdf

EFSA (European Food Safety Authority), 2021d. EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products. *EFSA supporting publication* 2021:EN-6472. doi:10.2903/sp.efsa.2021.EN-6472